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Supporting Information

Concise Total Synthesis of Enigmazole A

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General. Unless stated otherwise, all reactions were carried out in flame-dried glassware using anhydrous solvents under Argon. The solvents were purified by distillation over the following drying agents and were transferred under Ar: THF, Et_2O (Mg/anthracene), CH_2Cl_2, hexane, pentane, toluene (Na/K), MeOH (Mg, stored over MS 3 Å), EtOH (MS 3 Å), ethyl acetate (P_2O_5, filtered through dry Al_2O_3, stored over 4 Å MS); 1,4-dioxane, DMF, MeCN, NEt_3 and pyridine were dried by an adsorbtion solvent purification system based on molecular sieves. Thin layer chromatography (TLC): Macherey-Nagel precoated plates (POLYGRAM® SIL/UV254); Flash chromatography: Merck silica gel 60 (40–63 µm) with predistilled or HPLC grade solvents. NMR: Spectra were recorded on Bruker DPX 300, AV 400, AV 500 or AVIII 600 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: $\delta_C \equiv 77.2$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv 7.26$ ppm; CD_3OD: $\delta_C \equiv 49.0$ ppm; residual CHD_2OD: $\delta_H \equiv 3.31$ ppm). IR: Spectrum One (Perkin-Elmer) spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: ESQ3000 (Bruker), accurate mass determinations: Bruker APEX III FT-MS (7 T magnet) or Mat 95 (Finnigan). Optical rotations ($[\alpha]_D^{20}$) were measured with a Perkin-Elmer Model 343 polarimeter. LC-MS analyses were conducted on a Shimadzu LC-MS2020 instrument (pumps LC-20AD, autosampler SIL-20AC, column oven CTO-20AC, diode array detector SPD-M20A, controller CBM-20A, ESI detector and software Lab-solutions) with an ZORBAX Eclipse Plus C18 1.8 µm, 3.0 or 4.6 mm ID × 50 mm (Agilent). A binary gradient of MeCN or MeOH in water or aq. triethylammonium acetate buffer (10 mmol. pH 8) was used at a flow rate of 0.5 (3.0 mm ID) or 0.8 (4.6 mm ID) mL/min. The oven temperature was kept at 35 °C and the detection wave length at 254 nm. Preparative LC was performed with a Shimadzu LC-20A prominence system (pumps LC-20AP, column oven CTO-20AC, diode array detector SPD-M20A, fraction collector FRC-10A, controller CBM-20A and software LC-solution); conditions for each compound are specified below. Unless stated otherwise, all commercially available compounds (Alfa Aesar, Aldrich, Fluka, TCI) were used as received.

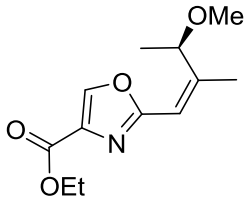
Oxazole Fragment

(*R*,*Z*)-4-Iodo-3-methylbut-3-en-2-ol (S1).[1] A suspension of (*R*)-(+)-3-butyn-2-ol (5.96 mL, 75.6 mmol) and copper(I) iodide (14.4 g, 75.6 mmol) in toluene (100 mL) was cooled to −78 °C. A solution of methylmagnesium bromide (1.4 M in THF/toluene 1:3, 378 mL, 529 mmol) was added over the course of 75 min. Once the addition was complete, the mixture was allowed to warm to ambient temperature and stirring was continued for 3.5 h. The mixture was then cooled to −40 °C before a solution of iodine (134 g, 529 mmol) in THF (140 mL) was slowly added via cannula. After stirring 1.5 h at room temperature, the reaction was carefully quenched by the addition of sat. aq. sodium thiosulfate (400 mL). The aqueous phase was extracted with Et_2O (3 × 200 mL) and the combined extracts were dried over $MgSO_4$, filtered and concentrated by distillation (in portions, 40 °C, ≥90 mbar, Vigreux column, collection flask cooled to −78 °C). The residue (200 mL) was purified by flash chromatography (pentane/Et_2O, 7:1 to 6:1) and the product containing fractions were concentrated by careful distillation (40 °C, ≥200 mbar) to yield the title compound (93% in Et_2O, 12.7 g, 74%) as a pale orange liquid. $[\alpha]_D^{20}$ = +12.3 (c = 2.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.89-5.88 (m, 1H), 4.77 (qd, *J* = 6.5, 2.8 Hz, 1H), 1.87 (d, *J* = 1.5 Hz, 3H), 1.79-1.78 (m, 1H) 1.25 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.4, 73.7, 72.6, 20.4, 18.4; IR (film): $\tilde{\nu}$ = 3331, 2973, 2916, 16134, 1441, 1369, 1278, 1134, 1102, 1073, 1037, 1021, 975, 902, 770 cm^{-1}; MS (EI) *m*/*z* (%): 127 (3), 85 (69),45 (57), 43 (100); HRMS (EI): *m*/*z*: calcd. for C_5H_9OI [*M*]: 211.9698, found: 211.9700.

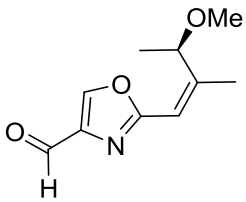
(*R*,*Z*)-1-Iodo-3-methoxy-2-methylbut-1-ene (5).[2] A solution of the alcohol **S1** (93% in Et_2O, 12.7 g, 55.7 mmol) in THF (80 mL) was added over 10 min to a suspension of sodium hydride (2.67 g, 111 mmol) and imidazole (379 mg, 5.57 mmol, 0.10 equiv) in THF (150 mL) at 0 °C. The mixture was allowed to reach ambient temperature and stirring was continued for 2 h before methyl iodide (31.6 g, 223 mmol) was added slowly. After an additional 2 h, the excess reagent was quenched with water (250 mL) and the aqueous layer was extracted with pentane (2 × 250 mL). The combined extracts were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated by careful distillation (25 °C, ≥350 mbar, Vigreux column, collection flask cooled to −78 °C). The residue (ca. 100 mL) was purified by flash chromatography (pentane/Et_2O, 20:1) and product-containing fractions were concentrated by distillation (30 °C, ≥300 mbar) to yield compound

5 as an yellowish liquid (95% in pentane, 8.44 g, 64%). $[\alpha]_D^{20}$ = +5.3 (c = 2.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.03-6.02 (m, 1H), 4.26 (q, *J* = 6.5 Hz, 1H), 3.22 (s, 3H), 1.79 (d, *J* = 1.5 Hz, 3H), 1.19 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.5, 80.9, 75.8, 56.4, 18.6, 18.1; IR (film): $\tilde{\nu}$ = 2978, 2928, 2820, 1613, 1441, 1369, 1339, 1279, 1205, 1144, 1114, 1094, 1064, 1030, 968, 865, 773. cm^{-1}; MS (EI) *m*/*z* (%): 195 (3), 127 (2), 99 (100), 31 (14); HRMS (EI): *m*/*z*: calcd. for $C_6H_{11}OI$ [*M*]: 225.9854, found: 225.9855.

Ethyl (*R*,*Z*)-2-(3-methoxy-2-methylbut-1-en-1-yl)oxazole-4-carboxylate (7).[2] In a pressure tube, palladium(II) acetate (265 mg, 1.18 mmol, 5 mol%) was added to a suspension of caesium carbonate (15.4 g, 47.3 mmol), ethyl-4-oxazolcarboxylate **6** (3.3 g, 23.6 mmol), alkenyl iodide **5** (95% in pentane, 8.44 g, 35.5 mmol) and 2-(dicyclohexylphosphino)biphenyl (829 mg, 2.36 mmol, 10 mol%) in 1,4-dioxane (65 mL). The mixture was stirred at 110 °C for 23 h. After cooling to ambient temperature, the suspension was filtered through Celite which was carefully rinsed with CH_2Cl_2 (50 mL). The filtrate was concentrated under reduced pressure (40 °C, ≥50 mbar) and the residue was purified by flash chromatography (hexanes/ethyl acetate, 20:1 to 4:1) to yield compound **7** (4.16 g, 74%) as a colorless oil. $[\alpha]_D^{20}$ = +41.7 (c = 1.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1H), 6.25 (s, 1H), 5.13 (q, *J* = 6.4 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.22 (s, 3H), 1.92 (d, *J* = 1.5 Hz, 3H), 1.37 (d, *J* = 7.0 Hz, 3H), 1.32 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.6, 161.2, 153.4, 142.9, 134.4, 112.9, 75.0, 61.4, 56.7, 19.6, 18.1, 14.5; IR (film): $\tilde{\nu}$ = 3154, 2981, 2932, 2821, 1743, 1720, 1654, 1575, 1562, 1447, 1370, 1332, 1316, 1279, 1217, 1178, 1109, 1025, 971, 947, 839, 771 cm^{-1}; MS (EI) *m*/*z* (%): 224 (100), 194 (7), 180 (3), 59 (9); HRMS (ESI): *m*/*z*: calcd. for $C_{12}H_{17}NO_4Na$ [*M*+Na^+]: 262.1049 found: 262.1051.

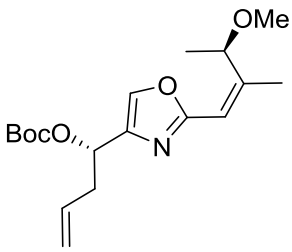


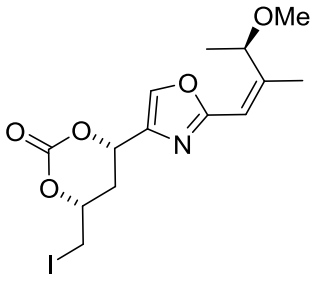
(*R*,*Z*)-2-(3-Methoxy-2-methylbut-1-enyl)oxazole-4-carbaldehyde (8).[2] A solution of oxazole **7** (4.20 g, 17.6 mmol) in CH_2Cl_2 (150 mL) was cooled to −90 °C and treated dropwise over 15 min with Dibal-H (1 M in toluene, 35.1 mL, 35.1 mmol). The mixture was stirred at −90 °C until TLC showed complete consumption of the starting material (ca. 20 min). The excess reagent was carefully quenched by the addition of methanol (15 mL) and sat. aq. potassium sodium tartrate (200 mL). The mixture was stirred for 18 h at 23 °C before the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL). The combined extracts were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated. The



residue was purified by flash chromatography (hexanes/ethyl acetate, 15:1 to 10:1) to give product **8** (2.74 g, 80%) as a yellowish oil. $[\alpha]_D^{20}$ = +46.8 (c = 2.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.93 (s, 1H), 8.16 (s, 1H), 6.23-6.22 (m, 1H), 5.24 (q, *J* = 6.5 Hz, 1H), 3.23 (s, 3H), 1.94 (d, *J* = 1.5 Hz, 3H), 1.32 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.7, 161.4, 154.7, 142.9, 141.7, 112.1, 74.9, 56.7, 19.3, 18.0; IR (film): $\tilde{\nu}$ = 3144, 3085, 2979, 2932, 2822, 1698, 1652, 1563, 1447, 1393, 1381, 1326, 1290, 1206, 1149, 1113, 1096, 1069, 833, 759 cm^{-1}; MS (EI) *m*/*z* (%): 195 (15), 180 (100), 59 (6); HRMS (ESI): *m*/*z*: calcd. for $C_{10}H_{13}NO_3Na$ [*M*+Na^+]: 218.0787 found: 218.0789.

(*S*)-1-(2-((R,Z)-3-Methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)but-3-en-1-ol (9). Powdered molecular sieves 4 Å (5 g, activated for 5 days at 120 °C) and titanium(IV) isopropoxide (411 µL, 1.39 mmol, 10 mol%) were added to a solution of (*S*)-(−)-1,1′-bi(2-naphthol) (398 mg, 1.39 mmol, 10 mol%) in CH_2Cl_2 (25 mL). The orange suspension was stirred at reflux temperature for 1 h before it was allowed to cool to ambient temperature. A solution of aldehyde **8** (2.71 g, 13.9 mmol) in CH_2Cl_2 (15 mL) was added. The mixture was cooled to −78 °C before allyltributylstannane (5.25 mL, 16.9 mmol) was added dropwise. After 3 days at −30 °C, TLC showed complete consumption of the starting material. The reaction was quenched with sat. aq. $NaHCO_3$ (25 mL) and the mixture allowed to reach ambient temperature. The suspension was filtered through a plug of Celite which was carefully rinsed with *tert*-butyl methyl ether (25 mL). The filtrate was concentrated until good separation of the layers was reached. The aq. phase was extracted with *tert*-butyl methyl ether (2 × 25 mL) and the combined extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/ethyl acetate, 15:1 to 4:1) to give the title compound (3.21g, 98%) as a pale yellow oil. The de > 95% was determined by analysis of the derived Mosher esters). $[\alpha]_D^{20}$ = +22.3 (c = 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (s, 1H), 6.19 (s, 1H), 5.84 (ddt, *J* = 17.2, 10.3, 7.1 Hz, 1H), 5.20-5.14 (m, 3H), 4.73 (dd, *J* = 7.3, 5.6 Hz, 1H), 3.22 (s, 3H), 2.69-2.62 (m, 1H), 2.59-2.52 (m, 1H), 2.39 (br s, 1H), 1.89 (d, *J* = 1.4 Hz, 3H), 1.30 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7, 151.1, 144.0, 134.0, 133.2, 118.8, 113.5, 75.0, 66.7, 56.7, 41.1, 19.4, 17.8; IR (film): $\tilde{\nu}$ = 3417, 2980, 2933, 1655, 1642, 1542, 1539, 1381, 1371, 1206, 1154, 1113, 1095, 1068, 915, 862. cm^{-1}; MS (EI) *m*/*z* (%): 237 (38), 222 (56), 204 (100); HRMS (ESI): *m*/*z*: calcd. for $C_{13}H_{19}NO_3Na$ [*M*+Na^+]: 260.1257 found: 260.1257.

***tert*-Butyl ((*S*)-1-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)but-3-en-1-yl) carbonate (10).**  Di-*tert*-butyl dicarbonate (7.30 g, 33.5 mmol) and 4-(dimethylamino)pyridine (1.02 g, 8.37 mmol) were added to a solution of the alcohol **9** (3.79 g, 17.7 mmol) in MeCN (150 mL). After stirring for 20 h, the mixture was concentrated and the residue was dissolved in *tert*-butyl methyl ether (100 mL) and water (100 mL). The layers were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (2 × 100 mL). The combined extracts were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 15:1 to 10:1) to yield the title compound (5.18 g, 92%) as a pale yellow oil. $[\alpha]_D^{20}$ = –8.8 (c = 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 0.4 Hz, 1H), 6.19-6.18 (m, 1H), 5.76 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.62 (t, *J* = 6.5 Hz, 1H), 5.21 (q, *J* = 6.5 Hz, 1H), 5.13 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.08-5.05 (m, 1H), 3.22 (s, 3H), 2.78 (ddt, *J* = 14.3, 6.6, 1.5 Hz, 1H), 2.71 (ddt, *J* = 14.2, 7.1, 1.2 Hz, 1H), 1.88 (d, *J* = 1.4 Hz, 3H), 1.47 (s, 9H), 1.31 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 153.1, 151.2, 140.1, 134.9, 133.0, 118.5, 113.4, 82.6, 74.9, 71.2, 56.9, 37.8, 28.0 (3C), 19.3, 17.8; IR (film): $\tilde{\nu}$ = 2980, 2933, 2820, 1740, 1644, 1544, 1449, 1369, 1342, 1280, 1254, 1163, 1095, 1036, 973, 919, 845, 793, 762 cm^{-1}; MS (EI) *m*/*z* (%): 337 (15.86), 281 (18.30), 220 (57.00), 204 (100), 117 (2); HRMS (ESI): *m*/*z*: calcd. for $C_{18}H_{27}NO_5Na$ [*M*+Na^+]: 360.1781 found: 360.1783.

(4*R*,6*S*)-4-(Iodomethyl)-6-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-1,3-dioxan-2-one (11).  A solution of olefin **10** (3.97 g, 11.8 mmol) in toluene (140 mL) was cooled to −90 °C and treated dropwise with a solution of IBr (1 M in CH_2Cl_2, 35.3 mL, 35.3 mmol) over 40 min (it was essential to store the IBr solution at 23 °C). After complete addition, stirring was continued until TLC showed complete consumption of the starting material (ca. 10 min). The excess reagent was quenched with sat. aq. $NaHCO_3$ (100 mL) and sat. aq. sodium thiosulfate (100 mL). After reaching ambient temperature, the layers were separated and the aq. phase was extracted with *tert*-butyl methyl ether (2 × 150 mL). The combined extracts were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash chromatography (hexanes/ethyl acetate, 2:1) to yield the title compound (2.58 g, 54%) as a pale yellow oil. When the reaction was performed with only 200 mg of **10**, a yield of 73%

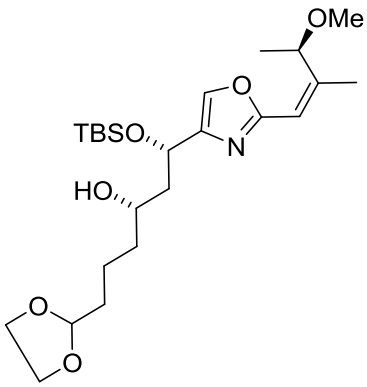
was obtained. $[\alpha]_D^{20}$ = +21.7 (c = 0.79, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 0.7 Hz, 1H), 6.19 (s, 1H), 5.50 (ddd, *J* = 11.7, 3.1, 0.7 Hz, 1H), 5.15 (q, *J* = 6.3 Hz, 1H), 4.64-4.58 (m, 1H), 3.46 (dd, *J* = 10.5, 4.4 Hz, 1H), 3.46 (dd, *J* = 10.5, 7.6 Hz, 1H), 3.23 (s, 3H), 2.78 (dt, *J* = 14.1, 3.19 Hz, 1H), 2.15 (dt, *J* = 14.3, 11.1 Hz, 1H), 1.92 (d, *J* = 1.7 Hz, 3H), 1.30 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 152.7, 147.9, 138.5, 134.9, 112.9, 74.9, 73.5, 69.5, 56.7, 33.0, 19.4, 17.9, 4.9; IR (film): $\tilde{\nu}$ = 3482, 3135, 2978, 2931, 2820, 1745, 1656, 1602, 1543, 1519, 1446, 1382, 1239, 1184, 1109, 1092, 1038, 971, 854, 760 cm^{-1}; MS (ESI) *m*/*z* (%): 430 (*M*+Na$^+$, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{14}H_{18}NO_5INa$ [*M*+Na$^+$]: 430.0121 found: 430.0120.

(*S*)-1-(2-((*R*,*Z*)-3-Methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-2-((*R*)-oxiran-2-yl)ethan-1-ol (S2). A solution of iodide **11** (2.11 g, 5.18 mmol) in MeOH (25 mL) was treated at 0 °C with potassium carbonate (2.15 g, 15.5 mmol). After stirring for 40 min, the mixture was diluted with *tert*-butyl methyl ether (25 mL) and excess reagent was quenched with sat. aq. ammonium chloride (50 mL). The aq. phase was extracted with *tert*-butyl methyl ether (2 × 25 mL) and the combined extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/ethyl acetate, 1:1) to yield the title compound (1.03 g, 79%) as a colorless oil. $[\alpha]_D^{20}$ = +28.0 (c = 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (s, 1H), 6.19 (s, 1H), 5.18 (q, *J* = 6.6 Hz, 1H), 4.94 (t, *J* = 5.7 Hz, 1H), 3.22 (s, 3H), 3.17-3.09 (m, 1H) 2.80 (dd, *J* = 4.8, 4.1 Hz, 1H), 2.72 (d, *J* = 4.3 Hz, 1H), 2.57 (dd, *J* = 5.9, 2.6 Hz, 1H), 2.27 (dt, *J* = 14.4, 4.5 Hz, 1H), 1.90 (d, *J* = 1.5 Hz, 3H), 1.92-1.81 (m, 1H), 1.30 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 151.3, 143.9, 133.4, 113.5, 75.0, 66.3, 65.8, 50.3, 47.0, 39.4, 19.4, 18.9; IR (film): $\tilde{\nu}$ = 3417, 2980, 2824, 2821, 1655, 1542, 1518, 1447, 1370, 1258, 1206, 1152, 1206, 1152, 1109, 1094, 1068, 1036, 971, 856, 753 cm^{-1}; MS (EI) *m*/*z* (%): 253 (13), 238 (53), 178 (100); HRMS (ESI): *m*/*z*: calcd. for $C_{13}H_{19}NO_4Na$ [*M*+Na$^+$]: 276.1206 found: 276.1208.

4-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-((*R*)-oxiran-2-yl)ethyl)-2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazole (12). TBSCl (1.25 g, 8.29 mmol) was added to a solution of alcohol **S2** (1.40 g, 5.53 mmol), imidazole (564 mg, 8.29 mmol) and 4-

(dimethylamino)-pyridine (67.5 mg, 0.553 mmol, 10 mol%) in CH_2Cl_2 (5.5 mL) at 0 °C. The mixture was stirred at ambient temperature until TLC showed complete consumption of the starting material (ca. 75 min). The mixture was diluted with *tert*-butyl methyl ether (20 mL) and excess reagent was quenched with sat. aq. ammonium chloride (30 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (2 × 30 mL). The combined extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane to hexanes/ethyl acetate, 30:1) to give the title compound (1.99 g, 98%) as a yellow oil. $[\alpha]_D^{20}$ = +13.2 (c = 0.44, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 0.7 Hz, 1H), 6.18 (dd, *J* = 1.2, 0.7 Hz, 1H), 5.21 (q, *J* = 6.2 Hz, 1H), 4.92 (td, *J* = 5.8, 1.1 Hz, 1H), 3.23 (s, 3H), 3.04 (m, 1H), 2.74 (t, *J* = 4.8 Hz, 1H), 2.50 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.11 (dt, *J* = 13.9, 5.8 Hz, 1H), 1.93 (dt, *J* = 13.9, 5.8 Hz, 1H), 1.89 (d, *J* = 1.4 Hz, 3H), 1.29 (d, *J* = 6.4 Hz, 3H), 0.9 (s, 9H), 0.1 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 150.7, 145.1, 133.7, 113.5, 74.9, 67.0, 56.6, 49.4, 47.0, 40.7, 25.8 (3C), 19.2, 18.2, 17.7, −4.6, −4.8; IR (film): $\tilde{\nu}$ = 2954, 2929, 2887, 2857, 2820, 1654, 1542, 1472, 1463, 1447, 1408, 1387, 1362, 1253, 1206, 1153, 1093, 1034, 1006, 968, 938, 913, 871, 833, 811, 775, 811, 775 cm^{-1}; MS (EI) *m*/*z* (%): 367 (5), 336 (2), 310 (100); HRMS (ESI): *m*/*z*: calcd. for $C_{19}H_{33}NO_4SiNa$ [*M*+Na^+]: 390.2071 found: 390.2067.

(1*S*,3*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-6-(1,3-dioxolan-2-yl)-1-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)hexan-3-ol (14).

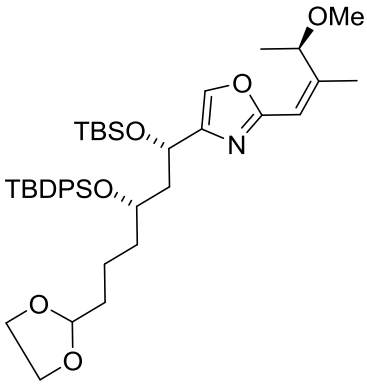


Preparation of the Grignard reagent **13**:[3] A solution of 2-(2-bromoethyl)-1,3-dioxolane (2.00 mL, 17.0 mmol) in THF (8.5 mL) was added over 30 min to a suspension of magnesium powder (1.04 g, 42.6 mmol) in THF (4.2 mL). The temperature was kept below 30 °C (water bath). After stirring for 1.5 h, the mixture was filtered through a syringe filter and the flask was rinsed with THF (2 mL) to give a yellowish solution of **13** (0.80 M in THF, 16.7 mL). The concentration was determined by titration using lithium chloride and iodine.[4]

Epoxide Opening: A suspension of copper(I) iodide (206 mg, 1.08 mmol, 20 mol%) in THF (30 mL) was cooled to −78 °C before an aliquot of the freshly prepared solution of the Grignard reagent **13** (0.80 M in THF, 10.2 mL, 8.12 mmol) was added dropwise. After stirring for 5 min, a solution of epoxide **12** (1.99 g, 5.41 mmol) in THF (30 mL) was added over 30 min. Once the addition was complete, the mixture was stirred at −40°C for 50 min. The

reaction was quenched with sat. aq. ammonium chloride (60 mL) and the mixture was allowed to reach ambient temperature. The layers were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (2 × 60 mL). The combined extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexanes/ethyl acetate, 5:1 to 2:1) to yield the title compound (2.35 g, 92%) as a pale yellow oil. $[\alpha]_D^{20}$ = −2.6 (c = 0.52, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 0.7 Hz, 1H), 6.17 (dd, *J* = 1.0, 0.7 Hz, 1H), 5.16 (q, *J* = 6.7 Hz, 1H), 4.93 (t, *J* = 6.7 Hz, 1H), 4.83 (t, *J* = 4.7 Hz, 1H), 3.97-3.78 (m, 5H), 3.49 (d, *J* = 2.7 Hz, 1H), 3.23 (s, 3H), 1.93 (ddd, *J* = 13.9, 9.1, 7.1 Hz, 1H), 1.59 (ddd, *J* = 13.9, 6.3, 2.7 Hz, 1H), 1.89 (d, *J* = 1.4 Hz, 3H), 1.68-1.43 (m, 6H), 1.29 (d, *J* = 6.3 Hz, 3H), 0.9 (s, 9H), 0.1 (s, 3H), –0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 151.3, 145.4, 133.6, 113.3, 104.8, 75.0, 69.5, 68.4, 65.0 (2C), 56.7, 45.2, 37.4, 34.0, 25.9 (3C), 20.3, 19.4, 18.2, 17.8, −4.5, −4.8; IR (film): $\tilde{\nu}$ = 3487, 2950, 3930, 2859, 1655, 1543, 1462, 1253, 1096, 970, 838, 778 cm^{-1}; MS (ESI) *m*/*z* (%): 492 (*M*+Na^+, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{24}H_{43}NO_6SiNa$ [*M*+Na^+]: 492.2751 found: 492.2751.

4-((5*S*,7*S*)-7-(3-(1,3-Dioxolan-2-yl)propyl)-2,2,3,3,10,10-hexamethyl-9,9-diphenyl-4,8-dioxa-3,9-disilaundecan-5-yl)-2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazole (S3). A solution of alcohol **14** (2.35 g, 5.00 mmol) in CH_2Cl_2 (45 mL) was cooled to 0 °C before 2,6-lutidine (1.75 mL, 15.0 mmol) and TBDPSOTf (1.77 mL, 5.75 mmol) were successively added. After stirring for 20 min at 0 °C, the reaction was quenched with sat. aq. ammonium chloride (50 mL), the layers were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (2 × 50 mL). The combined extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexanes/ethyl acetate, 15:1 to 6:1) to obtain the title compound (3.11 g, 88%) as a colorless oil. $[\alpha]_D^{20}$ = −9.0 (c = 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (td, *J* = 7.8, 1.3 Hz, 4H), 7.40-7.29 (m, 6H), 7.06 (s, 1H), 6.14 (s, 1H), 5.21 (q, *J* = 6.2 Hz, 1H), 4.80 (t, *J* = 6.6 Hz, 1H), 4.67 (t, *J* = 4.1 Hz, 1H), 3.90-3.77 (m, 5H), 3.17 (s, 3H), 2.01 (td, *J* = 6.8, 1.3 Hz, 2H), 1.88 (d, *J* = 1.4 Hz, 3H), 1.48-1.38 (m, 6H), 1.27 (d, *J* = 6.2 Hz, 3H), 1.02 (s, 9H), 0.81 (s, 9H), 0.01 (s, 3H), –0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6, 150.3, 144.9, 136.1 (2C), 136.0 (2C), 134.8, 134.6, 133.6, 129.6, 129.57, 129.55, 127.55 (2C), 127.54 (2C), 113.7, 104.7, 74.9, 70.6, 65.8, 64.9, 56.5, 44.0,



36.6, 34.0, 27.3 (3C), 26.0 (3C), 19.6, 19.3, 19.1, 18.3, 17.7, −4.3, −4.6; IR (film): $\tilde{\nu}$ = 2953, 2931, 2887, 2852, 1428, 1257, 1107, 1066, 972, 939, 837, 820, 776, 702 cm^{-1}; MS (ESI) *m*/*z* (%): 730 (*M*+Na^+, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{40}H_{61}NO_6SiNa$ [*M*+Na^+]: 730.3929 found: 730.3938.

(5*S*,7*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-((*tert*-butyldiphenylsilyl)oxy)-7-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)heptanal (15). 2,4,6-trimethylpyridine (1.10 mL, 8.31 mmol) and TMSOTf (1.00 mL, 5.54 mmol) were added to a solution of dioxolane **S3** (2.21 g, 2.77 mmol) in CH_2Cl_2 (50 mL) at 0 °C. After stirring for 1 h at this temperature, water (50 mL) was added and stirring continued for 2 h at ambient temperature. The layers were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 50 mL). The combined extracts were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash chromatography (hexanes/ethyl acetate, 20:1 to 15:1) to give the title compound (1.78 g, 97%) as a pale yellow oil. $[\alpha]_D^{20}$ = −10.4 (c = 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (t, *J* = 1.8 Hz, 1H), 7.64-7.60 (m, 4H), 7.42-7.30 (m, 6H), 7.11 (s, 1H), 6.15 (qd, *J* = 1.4, 0.8 Hz, 1H), 5.20 (q, *J* = 6.5 Hz, 1H), 4.79 (t, *J* = 6.5 Hz, 1H), 3.95-3.86 (m, 1H), 3.18 (s, 3H), 2.15-1.99 (m, 4H), 1.89 (d, *J* = 1.4 Hz, 3H), 1.61-1.42 (m, 4H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.04 (s, 9H), 0.81 (s, 9H), 0.01 (s, 3H), –0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.5, 160.0, 150.4, 145.0, 136.1 (2C), 136.0 (2C), 134.6, 134.4, 133.6, 129.7 (2C), 127.62 (2C), 127. 61 (2C), 113.6, 74.9, 70.1, 65.8, 56.6, 44.1, 43.8, 36.0, 27.2 (3C), 25.9 (3C), 19.6, 19.3, 18.2, 17.7, 17.2, −4.3, −4.7; IR (film): $\tilde{\nu}$ = 2953, 2930, 2891, 2857, 1727, 1655, 1589, 1544, 1472, 1462, 1428, 1388, 1361, 1252, 1205, 1078, 1068, 1005, 971, 938, 836, 777 cm^{-1}; MS (ESI) *m*/*z* (%): 686 (*M*+Na^+, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{38}H_{57}NO_5Si_2Na$ [*M*+Na^+]: 686.3667 found: 686.3664.

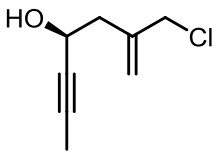
Allyltin Fragment

2-Butynal (18). Tetrabutylammonium chloride (3.97 g, 14.3 mmol, 0.10 equiv) and TEMPO (2.23, 14.3 mmol, 0.10 equiv) were added to a solution of 2-butyn-1-ol (10.0 g, 143 mmol) in a mixture of CH_2Cl_2 (200 mL) and aq. carbonate buffer (100 mL 0.5 M $NaHCO_3$ and 100 mL 0.05 M K_2CO_3). *N*-Chlorosuccinimide (30.5 g, 228 mmol) was added in several portions,[5] causing a slight exotherm and an evolution of gas, which was discharged by passing the gas stream through a wash bottle containing aq. sodium hydroxide solution (1 M). After stirring for 17 h, the aqueous phase was extracted with CH_2Cl_2 (4 × 75 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was purified by distillation (25 °C, ≤ 150 mbar, Vigreux column, the collection flask was cooled to −78 °C) to obtain the title compound (60% in CH_2Cl_2, 10.9 g, 67%) as a colorless solution. The compound is very sensitive and was kept under argon at −78 °C (decomposition commences with appearance of a pink coloration). The analytical data were in full agreement with those reported in literature.[6] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.15 (q, *J* = 1.0 Hz, 1H), 2.07 (d, *J* = 0.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ =177.3, 95.1, 81.1, 4.46.

Tributyl(2-(chloromethyl)allyl)stannane (17).[7] A solution of diisopropylamine (4.00 mL, 28.5 mmol) in THF (60 mL) was cooled to 0 °C before it was treated dropwise with *n*-BuLi (1.6 M in hexanes, 16.2 mL, 25.9 mmol). After stirring for 5 min, tributyltin hydride (6.28 mL, 23.3 mmol) was added and stirring continued for 15 min at 0 °C. The resulting solution was then added over the course of 1 h to a solution of 3-chloro-2-chloromethyl-1-propene (3.00 mL, 25.9 mmol) in pentane (100 mL) at −78 °C. The mixture was stirred for 1 h at −78 °C before the reaction was quenched with water (100 mL). The mixture was diluted with hexanes/ethyl acetate (10:1, 240 mL), the organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated and the residue was purified by flash chromatography (hexanes) to yield the title compound (4.78 g, 49%) as a colorless liquid. The spectral data were in full agreement with those reported in literature.[8] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.84 (dt, *J* = 1.3, 0.7 Hz, $J_{H\text{-}Sn}$ = 17.3 Hz, 1H), 4.71 (dt, *J* = 1.3, 0.7 Hz, $J_{H\text{-}Sn}$ = 17.9 Hz, 1H), 3.96 (d, *J* = 0.9 Hz, $J_{H\text{-}Sn}$ = 5.8 Hz, 2H) 1.89 (d, *J* = 0.9 Hz, $J_{H\text{-}Sn}$ = 57.9 Hz, 2H), 1.60-1.36 (m, 6H), 1.36-1.22 (m, 6H), 0.95-0.79 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8 ($J_{H\text{-}Sn}$ = 39.0 Hz), 110.0 ($J_{H\text{-}Sn}$ = 36.4 Hz), 50.4 ($J_{H\text{-}Sn}$ = 8.6 Hz), 29.2 ($J_{H\text{-}Sn}$ = 20.1 Hz), 27.5 ($J_{H\text{-}Sn}^{117}$ = 54.0 Hz, $J_{H\text{-}Sn}^{119}$ = 56.0 Hz), 16.0 ($J_{H\text{-}Sn}^{117}$ = 221.0 Hz,

$J_{H\text{-}Sn}^{119}$ = 231.3 Hz), 13.9, 9.8 ($J_{H\text{-}Sn}^{117}$ = 306.5 Hz, $J_{H\text{-}Sn}^{119}$ = 320.8 Hz); ^{119}Sn NMR (150 MHz, $CDCl_3$): δ = −12.9.

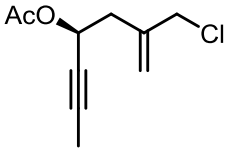
(*S*)-2-(Chloromethyl)hept-1-en-5-yn-4-ol (19). Powdered molecular sieve 4 Å (5 g, activated for 5 days at 120 °C) and titanium(IV) isopropoxide (334 µL, 1.13 mmol, 0.10 equiv) were added to a solution of (*S*)-(−)-1,1′-bi(2-naphthol) (323 mg, 1.13 mmol, 0.10 mmol) in CH_2Cl_2 (25 mL). The orange suspension was stirred at reflux temperature for 1 h. After reaching ambient temperature, a solution of aldehyde **18** (75% in CH_2Cl_2, 1.02 g, 11.3 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was cooled to −78 °C before stannane **17** (4.48 g, 13.5 mmol) was added dropwise. After stirring for 3 d at −30 °C, TLC showed complete consumption of the starting material. The reaction was quenched with sat. aq. potassium sodium tartrate (50 mL) and stirring was continued for 1 h at room temperature. The suspension was filtered through a plug of Celite, which was carefully rinsed with *tert*-butyl methyl ether (25 mL). The volume of the filtrate was reduced, the layers were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (2 × 25 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/ethyl acetate, 10:1 to 4:1) to give the title compound (1.50 g, 84%) as a colorless liquid. $[\alpha]_D^{20}$ = −28.7 (c = 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.29 (s, 1H), 5.13 (s, 1H), 4.54-4.50 (m, 1H), 4.13 (s, 2H), 2.58 (d, *J* = 6.7 Hz, 2H), 1.84 (d, *J* = 1.8 Hz, 3H), 1.75 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.2, 118.3, 81.9, 79.8, 61.4, 48.5, 41.8, 3.7; IR (film): $\tilde{\nu}$ = 3367, 2919, 2930, 1646, 1437, 1258, 1136, 1113, 1006, 913, 851, 749 cm^{-1}; MS (EI) *m*/*z* (%): 123 (2), 90 (3), 69 (100); HRMS (CI): *m*/*z*: calcd. for $C_8H_{15}NO$ [M+NH_4^+]: 176.0842, found: 176.0840.



The absolute configuration was determined by Mosher ester analysis, the *ee* was determined after the next step by HPLC on a chiral column.

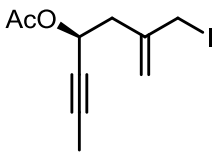
The other enantiomer, (R)-19, was obtained analogously using (*R*)-(−)-1,1′-bi(2-naphthol) as chiral ligand; $[\alpha]_D^{20}$ = +25.8 (c = 1.08, $CHCl_3$).

(*S*)-2-(Chloromethyl)hept-1-en-5-yn-4-yl acetate (S4). 4-(Dimethylamino)pyridine (116 mg, 0.946 mmol, 10 mol%), triethylamine (2.64 mL, 18.9 mmol) and acetic anhydride (1.34 mL, 14.2 mmol) were added to a solution of alcohol **19** (1.50 g, 9.46 mmol) in CH_2Cl_2 (60 mL). After stirring for 1 h, the mixture was carefully evaporated (40 °C, ≥ 600 mbar) and the residue was purified by

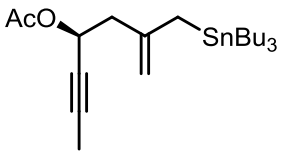


flash chromatography (pentane/Et_2O 10:1) to furnish the title compound (1.77 g, 93%) as a colorless liquid. The enantiomeric purity (e.e. ≥ 95%) was determined by HPLC analysis on a chiral column (150 × 4.6 mm Chiralpak IC-3, 3 μm, *n*-heptane/2-propanol 99:1 (v/v), 1.0 mL/min, 293 K). $[\alpha]_D^{20}$ = −75.3 (c = 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51-5.48 (ddq, *J* = 8.4 6.4, 2.2 Hz, 1H), 5.25 (d, *J* = 1.1 Hz, 1H), 5.08 (d, *J* = 1.1 Hz, 1H), 4.10 (d, *J* = 11.8 Hz, 1H), 4.08 (d, *J* = 11.8 Hz, 1H), 2.70-2.57 (m, 2H), 2.06 (s, 3H), 1.83 (d, *J* = 2.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 140.3, 118.6, 82.7, 76.3, 62.9, 48.2, 38.8, 21.2, 3.7; IR (film): $\tilde{\nu}$ = 2930, 2923, 1739, 1647, 1437, 1371, 1230, 1160, 1020, 989, 914, 752 cm^{-1}; MS (ESI) *m*/*z* (%): 223 (*M*+Na^+, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{10}H_{13}O_2ClNa$ [*M*+Na^+]: 223.0496, found: 223.0494.

(*S*)-2-(Iodomethyl)hept-1-en-5-yn-4-yl acetate (S5). Sodium iodide (2.19 g, 14.6 mmol) was added to a solution of chloride **S4** (2.18 g, 10.8 mmol) in acetone (15 mL) and the resulting suspension was stirred at reflux temperature for 20 h. After cooling to ambient temperature, the excess reagent was quenched with sat. aq. sodium thiosulfate (25 mL) and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 × 25 mL), and the combined extracts were dried over Mg_2SO_4, filtered and concentrated (40 °C, ≥150 mbar). The crude material was purified by flash chromatography (pentane/Et_2O, 20:1 to 10:1) to yield the title compound (2.78 g, 88%) as a pale yellow liquid. $[\alpha]_D^{20}$ = −38.9 (c = 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.50-5.49 (m, 1H), 5.35 (d, *J* = 0.8 Hz,1H), 5.01 (d, *J* = 0.8 Hz, 1H), 4.01 (dd, *J* = 9.6, 0.4 Hz, 1H), 3.97 (d, *J* = 9.6 Hz, 1H), 2.71 (ddd, *J* = 14.4, 6.1, 0.8 Hz, 1H), 2.63 (ddd, *J* = 14.4, 7.1, 0.8 Hz, 1H), 2.06 (s, 3H), 1.83 (d, *J* = 2.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 141.8, 117.7, 82.7, 76.3, 62.9, 39.8, 21.2, 10.4, 3.8; IR (film): $\tilde{\nu}$ = 2956, 2920,1739, 1636, 1431, 1371, 1230, 1157, 1020, 986, 914 cm^{-1}; MS (EI) *m*/*z* (%): 232 (72), 123 (47), 105 (100); HRMS (ESI): *m*/*z*: calcd. for $C_{10}H_{13}O_2INa$ [*M*+Na^+]: 314.9852, found: 314.9852.



(*S*)-2-((Tributylstannyl)methyl)hept-1-en-5-yn-4-yl acetate (20). Hexabutylditin (5.53 mL, 10.9 mmol) and tris-(dibenzylideneacetone)-dipalladium(0) (110 mg, 0.12 mmol, 1.7 mol%) were added to a suspension of iodide **S5** (2.13 g, 7.29 mmol) in THF (10 mL). Argon was bubbled through the green-black suspension for 30 min, before the mixture was stirred for 3 h at 55 °C. Because TLC showed unreacted starting material, the same amount of tris-(dibenzylideneacetone)-

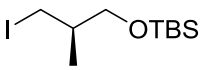


dipalladium(0) (1.7 mol%) was added. Stirring at reflux temperature was continued for an additional 1.5 h before the reaction was quenched with sat. aq. $NaHCO_3$ (25 mL). The mixture was filtered through a plug of Celite which was rinsed with *tert*-butyl methyl ether (2 x 25 mL). The layers were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 x 25 mL). The combined extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by repeated flash chromatography (hexanes + 2% triethylamine) to yield the title compound (2.42 g, 73%) as a colorless liquid. $[\alpha]_D^{20} = -28.1$ (c = 0.98, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.49 (t, *J* = 7.2 Hz, 1H), 4.64-4.61(m, 1H), 4.55-4.53 (m, 1H), 2.35 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.31 (dd, *J* = 14.1, 6.2 Hz, 1H), 2.06 (s, 3H), 1.84 (d, *J* = 1.6 Hz, 3H), 1.80 (s, 2H), 1.56-1.39 (m, 6H), 1.30 (sext, *J* = 7.2 Hz, 6H), 0.89 (t, *J* = 7.7 Hz, 9H), 0.87 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 144.6, 108.4, 82.2, 77.1, 63.3, 44.0, 29.3 ($J_{H\text{-}Sn}$ = 10.1 Hz, 3C), 27.5 ($J_{H\text{-}Sn}^{117}$ = 26.9 Hz, $J_{H\text{-}Sn}^{119}$ = 28.1 Hz, 3C), 21.3, 19.1, 13.9 (3C), 9.6 ($J_{H\text{-}Sn}^{117}$ = 151.6 Hz, $J_{H\text{-}Sn}^{119}$ = 158.7 Hz, 3C), 3.9; IR (film): $\tilde{\nu}$ = 2956, 2923, 2853, 2872, 2742, 1629, 1464, 1371, 1230, 1018, 961, 866 cm^{-1}; MS (EI) *m*/*z* (%): 456 (2), 399 (13), 179 (100), 57 (45), 43 (29); HRMS (ESI): *m*/*z*: calcd. for $C_{22}H_{40}O_2SnNa$ [*M*+Na^+]: 479.1956, found: 479.1954.

The enantiomeric building block (*R*)-**20** was prepared by following the same route.

Acid Fragment

(*R*)-*tert*-Butyl(3-iodo-2-methylpropoxy)dimethylsilane (25).[9] Sodium iodide (20.0 g, 133 mmol) was added to a solution of the (*R*)-3-bromo-2-methylpropan-1-ol **24** (5.00 g, 32.6 mmol) in acetone (60 mL). The mixture was stirred at reflux temperature for 18 h. Water (20 mL) was added and the acetone was removed under reduced pressure and the resulting mixture was extracted with CH_2Cl_2 (2 x 30 mL). The combined extracts were washed with aq. sat. ammonium thiosulfate (2 x 30 mL) and brine, dried over Na_2SO_4, filtered and concentrated. The resulting crude product was directly used in the next step.



Imidazole (2.40 g, 35.8 mmol) and TBSCl (5.40 g, 35.8 mmol) were added at 0 °C to a solution of crude (*R*)-3-iodo-2-methylpropan-1-ol described above (6.30 g, 32.6 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred for 3 h at 0 °C, before it was filtered and washed with pentane (50 mL). The combined filtrates were evaporated, the residue was suspended in pentane and the resulting mixture filtered again through Celite, rinsing with pentane. The

combined filtrate was evaporated and the residue purified by flash chromatography (hexane) to give the title compound (8.54 g, 85%) as a colorless oil. $[\alpha]_D^{20}$ = −10.5 (c = 4.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (dd, *J* = 10.1, 4.9 Hz, 1H), 3.39 (dd, *J* = 10.1, 6.7 Hz, 1H), 3.30 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.24 (dd, *J* = 9.6, 5.4 Hz, 1H), 1.67-1.59 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.060 (s, 3H), 0.059 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 66.9, 37.6, 26.1, 18.5, 17.5, 13.9, –5.1 (2C); IR (film): $\tilde{\nu}$ = 2955, 2929, 2894, 2857, 1470, 1475, 1419, 1386, 1361, 1329, 1251, 1197, 1181, 1136, 1098, 1065, 1035, 1006, 937, 835, 773 cm^{-1}; MS (EI) *m*/*z* (%): 257 (100); HRMS (CI): *m*/*z*: calcd. for $C_{10}H_{24}OISi$ [M^++H]: 315.0641 found: 315.0642.

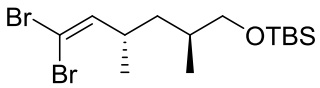
(2*S*,4*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-2,4-trimethylpentanamide (27).[10] *n*-BuLi (1.6 M in hexanes, 48.8 mL, 78.1 mmol) was added dropwise at −78 °C to a stirred suspension of lithium chloride (flame-dried, 12.8 g, 308 mmol) and diisopropylamine (11.8 mL, 84.0 mmol) in THF (48 mL). The mixture was warmed to 0 °C for 5 min before it was cooled again to −78 °C. A solution of (*R*,*R*)-(−)-pseudoephedrine propionamide **26** (8.0 g, 36.9 mmol) in THF (102 mL) was added dropwise and the resulting mixture was stirred for 1 h at −78 °C, 30 min at 0 °C and 5 min at ambient temperature. A solution of **25** (7.2 g, 22.8 mmol) in THF (10 mL) was added dropwise at 0 °C and stirring continued for 22 h at room temperature. The reaction was quenched with aq. sat. ammonium chloride (100 mL) and the aqueous phase was extracted with ethyl acetate (2 x 100 mL). The combined extracts were washed with brine, dried over Na_2SO_4 filtered and concentrated. The remaining residue was purified by flash chromatography (hexanes/ethyl acetate, 3:1) to give the title compound as a colorless solid (9.1 g, 98%) (mixture of rotamers, 3:1, NMR). $[\alpha]_D^{20}$ = −53.0 (c = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (major rotamer): δ = 7.35-7.29 (m, 5H), 3.60 (t, *J* = 7.2 Hz, 1H), 4.42 (br s, 1H), 3.39 (dd, *J* = 9.7, 5.2 Hz, 1H), 3.31 (dd, *J* = 9.7, 6.1 Hz, 1H), 2.85 (s, 3H), 2.71 (q, *J* = 7.0 Hz, 1H), 1.74 (oct, *J* = 6.5 Hz, 1H), 1.41-1.37 (m, 2H), 1.12 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.020 (s, 3H), 0.018 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (major rotamer): δ = 179.5, 142.8, 128.4 (2C), 127.7, 126.5 (2C), 76.7, 68.5 (2C), 37.6, 34.6, 33.7, 26.1 (3C), 18.6, 17.4, 17.1, 14.6, −5.2 (2C) (one carbon is missing due to signal overlap); IR (film): $\tilde{\nu}$ = 3374, 2955, 2930, 2857, 1620, 1471, 1461, 1408, 1251, 1087, 835, 774, 701 cm^{-1}; MS (EI) *m*/*z* (%): 392 (3), 350 (56), 300 (16), 243 (100); HRMS (ESI): *m*/*z*: calcd. for $C_{23}H_{41}NO_3SiNa$ [M+Na^+]: 430.2747 found: 430.2751.

(2*S*,4*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylpentan-1-ol (S6). *n*-BuLi (1.6 M in hexanes, 55.8 mL, 89.2 mmol) was added at −78 °C over 15 min to a stirred solution of diisopropylamine (13.3 mL, 95.5 mmol) in THF (92 mL). The mixture was stirred at this temperature for 10 min and for another 10 min at 0 °C. Borane-ammonia complex (90%, 3.10 g, 100 mmol) was then added and stirring continued for 15 min at 0 °C and for additional 15 min at ambient temperature. The mixture was cooled to 0 °C before a solution of amide **27** (9.00 g, 22.3 mmol) in THF (160 mL) was added over 15 min. Stirring was continued for 2 h at ambient temperature before the excess reagent was quenched at 0°C with aq. sat. ammonium chloride (150 mL). The aqueous layer was extracted with *tert*-butyl methyl ether (3 × 100 mL) and the combined extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexanes/ethyl acetate, 10:1) to obtain the title compound as a colorless syrup (4.90 g, 89%). $[\alpha]_D^{20}$ = −24.7 (c = 1.59, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.5-3.42 (m, 2H), 3.40 (dd, *J* = 6.3, 1.8 Hz, 2H), 1.78-1.67 (m, 2H), 1.47 (t, *J* = 5.9 Hz, 1H), 1.21 (ddd, *J* = 13.6, 8.8, 4.8 Hz, 1H), 1.12 (ddd, *J* = 13.6, 8.8, 4.8 Hz, 1H), 0.89 (s, 9H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.3, 69.2, 37.0, 33.3, 33.1, 26.2 (3C), 18.5, 16.8, 16.7, −5.1 (2C); IR (film): $\tilde{\nu}$ = 3375, 2954, 2929, 2857, 1620, 1471, 1454, 1405, 1095, 1050, 836, 774, 701 cm^{-1}; MS (EI) *m*/*z* (%): 215 (1), 189 (1), 55 (100); HRMS (CI): *m*/*z*: calcd. for $C_{13}H_{31}NO_2Si$ [*M*+H$^+$]: 247.2093 found: 247.2093.

((2*S*,4*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylpentanal (28). A suspension of *N*-methylmorpholine-*N*-oxide monohydrate (1.41 g, 10.4 mmol) and powdered molecular sieves (4 Å, 4 g) in CH_2Cl_2 (66 mL) was stirred for 10 min before a solution of alcohol **S6** (2.00 g, 8.1 mmol) in CH_2Cl_2 (32 mL) and tetra-*N*-propylammonium perruthenate (140 mg, 0.39 mmol, 5 mol%) were successively added. The resulting mixture was stirred for 30 min before it was filtered through a pad of Celite, which was carefully rinsed with CH_2Cl_2 (50 mL). The combined filtrates were evaporated and the residue was purified by a flash chromatography (hexanes/ethyl acetate, 5:1) to yield the title compound (1.72 g, 88%), which was immediately used in the next reaction. The recorded spectra data were in full agreement with those reported in literature.[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.59 (d, *J* = 2.0 Hz, 1H), 3.43 (dd, *J* = 9.8, 6.0 Hz, 1H), 3.39 (dd, *J* = 9.8, 6.0 Hz, 1H), 2.45-2.36 (m, 1H), 1.71-1.63 (m, 1H), 1.47 (ddd, *J* = 13.7, 8.3, 6.0 Hz, 1H), 1.39 (ddd, *J*

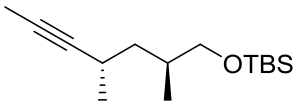
= 13.7, 8.3, 5.7 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.86 (s, 9H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.3, 68.2, 44.2, 34.0, 33.3, 26.0 (3C), 18.3, 16.6, 13.5, −5.3 (2C).

***tert*-Butyl(((2*S*,4*S*)-6,6-dibromo-2,4-dimethylhex-5-en-1-yl)oxy)dimethylsilane (29).** Zinc



powder (835 mg, 12.8 mmol) and triphenylphosphine (3.43 g, 13.1 mmol) were added to a solution of tetrabromomethane (4.34 g, 13.1 mmol) in CH_2Cl_2 (70 mL). After stirring for 18 h, a solution of aldehyde **28** (1.60 g, 6.54 mmol) in CH_2Cl_2 (20 mL) was slowly added and stirring was continued for 5 h. The mixture was poured into a beaker containing hexanes and the resulting precipitate was filtered off. Evaporation of the filtrate and purification of the residue by flash chroamtography (hexanes/ethyl acetate, 5:1) gave the title compound as a colorless syrup (1.93 g, 74%). $[\alpha]_D^{20}$ = +4.2 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.19 (d, J = 8.9 Hz, 1H), 3.44 (dd, *J* = 9.8, 5.4 Hz, 1H), 3.40 (dd, *J* = 9.8, 5.9 Hz, 1H), 2.56-2.48 (m, 1H), 1.69-1.53 (m, 1H), 1.42 (dt, *J* = 13.5, 6.8 Hz, 1H), 1.12 (dt, *J* = 14.7, 7.3 Hz, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9, 87.2, 67.8, 39.6, 36.2, 33.6, 26.2 (3C), 19.4, 18.5, 17.4, −5.1 (2C); IR (film): $\tilde{\nu}$ = 2956, 2929, 2827, 1471, 1461, 1251, 1095, 1080, 1006, 836, 774, 667 cm^{-1}; MS (EI) *m*/*z* (%): 343 (45), 107 (100); HRMS (CI): *m*/*z*: calcd. for $C_{14}H_{29}OBrSi$ [*M*+H$^+$]: 399.0354 found: 399.0350.

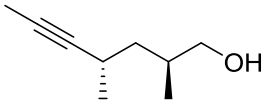
***tert*-Butyl(((2*S*,4*S*)-2,4-dimethylhept-5-yn-1-yl)oxy)dimethylsilane (S7).** *n*-BuLi (1.6 M in



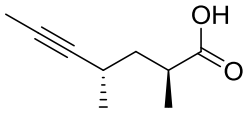
hexanes, 6.93 mL, 11.1 mmol) was added at −78 °C to a solution of dibromo-olefin **29** (1.93 g, 4.82 mmol) in THF (18 mL). The mixture was stirred at this temperature for 1 h and for 1 h at 23 °C. Iodomethane (0.81 mL, 13.0 mmo) was introduced and stirring continued for 2.5 h. The reaction was quenched with aq. sat. ammonium chloride (20 mL) and the aqueous phase was extracted with Et_2O (2 x 20 mL). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography (hexane to hexanes/ethyl acetate, 10:1) to obtain the title compound as a colorless oil (1.19 g, 97%, d.r. ≥ 95:5). $[\alpha]_D^{20}$ = +24.7 (c = 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.48 (dd, *J* = 9.7, 5.2 Hz, 1H), 3.39 (dd, *J* = 9.7, 6.2 Hz, 1H), 2.48-2.39 (m, 1H), 1.48-1.76 (m, 1H), 1.78 (d, *J* = 2.4 Hz, 3H), 1.41 (ddd, *J* = 13,4, 7.1, 6.7 Hz, 1H), 1.23 (ddd, *J* = 14,7, 8.7, 6.6 Hz, 1H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 84.4, 75.5, 67.7, 41.2, 33.8, 26.1 (3C), 23.9, 21.8,

18.5, 17.6, 3.7, −5.2, −5.1; IR (film): $\tilde{\nu}$ = 2956, 2929, 2857, 1471, 1388, 1361, 1251, 1092, 1019, 1006, 939, 835, 773, 666 cm^{-1}; MS (EI) *m*/*z* (%): 197 (13), 75 (100); HRMS (CI): *m*/*z*: calcd. for $C_{15}H_{31}OSi$ [*M*+H^+]: 255.2144 found: 255.2144.

(2*S*,4*S*)-2,4-Dimethylhept-5-yn-1-ol (S8). Tetrabutylammonium fluorode (1 M in THF, 8.17 mL, 8.17 mmol) was added to a solution of alkyne **S7** (1.04 g, 4.09 mmol) in THF (6.0 mL). The mixture was stirred for 18 h before the reaction was quenched with aq. sat. ammonium chloride (5 mL) and extracted with *tert*-butyl methyl ether (2 x 10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The remaining crude material was purified by flash chromatography (hexanes/ethyl acetate, 5:1) to yield **S8** as a colorless liquid (550 mg, 3.92 mmol, 96%, *d.r.* ≥ 95:5). $[\alpha]_D^{20}$ = +24.4 (c = 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.53 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.42 (dd, *J* = 10.5, 6.0 Hz, 1H), 2.49-2.42 (m, 1H), 1.84 (oct, *J* = 6.5 Hz, 1H), 1.75 (d, *J* = 2.5 Hz, 3H), 1.72 (br s, 1H), 1.39 (ddd, *J* = 13,4, 7.2, 6.1, 1H), 1.30 (ddd, *J* = 14,9, 8.6, 6.2, 1H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 84.1, 75.9, 67.7, 41.1, 33.7, 23.6, 21.7, 17.4, 3.6; IR (film): $\tilde{\nu}$ = 3323, 2960, 2921, 2873, 1453, 1375, 1043, 999, 977, 943, 757, 667 cm^{-1}; MS (EI) *m*/*z* (%): 67 (100), 31 (14); HRMS (CI): *m*/*z*: calcd. for $C_9H_{17}O$ [*M*+H^+]: 141.1279, found: 141.1277.



(2*S*,4*S*)-2,4-Dimethylhept-5-ynoic acid (30). Tetra-*n*-propylammonium perruthenate (96.5 mg, 275 µmol, 10 mol%) was added to a solution of *N*-methylmorpholine-*N*-oxide monohydrate (3.22 g, 27.5 mmol) and alcohol **S8** (385 mg, 2.75 mmol) in MeCN (5.6 mL). After stirring for 45 min, the mixture was filtered through a pad of Celite, which was carefully rinsed with ethyl acetate (10 mL). The combined filtrates were evaporated and the crude product was purified by flash chromatography (hexanes/ethyl acetate, 8:1) to give the title compound as a colorless liquid (391 mg, 92%, d.r. ≥ 95:5). $[\alpha]_D^{20}$ = +108.2 (c = 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.82-2.73 (m, 1H), 2.52-2.43 (m, 1H), 1.78 (ddd, *J* = 14,8, 9.8, 4.8 Hz, 1H), 1.77 (d, *J* = 2.33 Hz, 3H), 1.13 (ddd, *J* = 14,8, 10.4, 4.5 Hz, 1H), 1.23 (d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.9, 82.9, 76.7, 41.2, 37.9, 24.6, 21.9, 18.2, 3.67; IR (film): $\tilde{\nu}$ = 3100, 2972, 2921, 1706, 1456, 1377, 1248, 945 cm^{-1}; MS



(EI) *m*/*z* (%): 154 (1), 109 (26), 98 (100), 74 (37), 45 (7); HRMS (EI): *m*/*z*: calcd. for $C_9H_{14}O_2$ [M^+]: 154.0993, found: 154.0993.

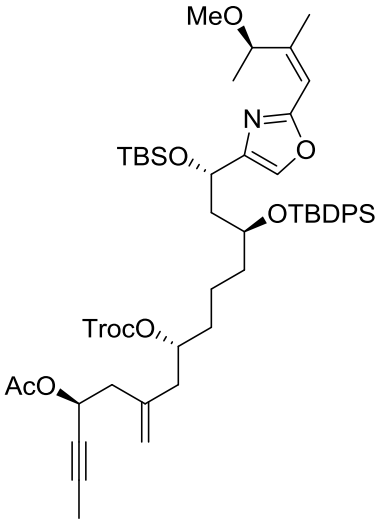
Completion of the Total Synthesis

(4*S*,8*R*,12*S*,14*S*)-14-((*tert*-Butyldimethylsilyl)oxy)-12-((*tert*-butyldiphenylsilyl)oxy)-8-hydroxy-14-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl) oxazol-4-yl)-6-methylenetetradec-2-yn-4-yl acetate (22). Boron tribromide (1 M in CH_2Cl_2, 3.39 mL, 3.39 mmol) was added at 0 °C to a solution of (*S*,*S*)-1,2-diphenyl-1,2-ethylenediamine bis(toluenesulfonamide) (1.76 g, 3.39 mmol)[12] in CH_2Cl_2 (40 mL). The mixture was stirred for 10 min at 0 °C and for 1 h at ambient temperature before all volatile materials were removed in high vacuum.

Allyl stannane **20** (1.80 g, 3.95 mmol) was added dropwise at 0 °C to a solution of the residue in CH_2Cl_2 (40 mL). After stirring for 17 h at ambient temperature, the mixture was cooled to −78°C and a solution of aldehyde **15** (1.50 g, 2.26 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 5 min. The mixture was stirred for 2 h before the reaction was quenched with aq. phosphate buffer (pH 7, 50 mL). Water (50 mL) was introduced and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated. The residue was suspended in Et_2O (20 mL) and the colorless solid was filtered off to recover the chiral diamine ligand. The filtrate was evaporated and the residue was purified by flash chromatography (hexanes/ethyl acetate, 10:1 to 3:1) to give the title compound (1.79 g, 95%, *d.r.* > 10:1) as a colorless oil. $[\alpha]_D^{20}$ = −20.9 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.62 (m, 2H), 7.59 (m, 2H), 7.37 (m, 1H), 7.36 (m, 1H), 7.31 (m, 2H), 7.29 (m, 2H), 7.08 (d, *J* = 0.5 Hz, 1H), 6.14 (qd, *J* = 1.4, 1.0 Hz, 1H), 5.45 (ddq, *J* = 7.8, 6.0, 2.2 Hz, 1H), 5.19 (qd, *J* = 6.5, 0.8 Hz, 1H), 4.95 (dt, *J* = 1.4, 1.2 Hz, 1H), 4.90 (d, *J* = 1.1 Hz, 1H), 4.81 (td, *J* = 6.7, 0.7 Hz, 1H), 3.84 (tdd, *J* = 6.2, 5.8, 5.1 Hz, 1H), 3.52 (dddt, *J* = 9.4, 7.6, 4.4, 3.2 Hz, 1H), 3.15 (s, 3H), 2.45 (ddd, *J* = 14.4, 7.8, 0.8 Hz, 1H), 2.40 (ddd, *J* = 14.4, 6.0, 0.9 Hz, 1H), 2.14 (ddd, *J* = 14.3, 3.3, 1.2 Hz, 1H), 2.03 (s, 3H), 2.01 (t, *J* = 6.7 Hz, 2H), 1.95 (ddd, *J* = 14.3, 9.4, 0.5 Hz, 1H), 1.86 (d *J* = 1.5 Hz, 3H), 1.82 (d, *J* = 2.2 Hz, 3H), 1.63 (d, *J* = 3.1 Hz, 1H), 1.47 (m, 1H), 1.38 (m, 1H), 1.32 (m, 1H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.24 (m, 1H), 1.20 (m, 1H), 1.15 (m, 1H), 1.01 (s, 9H), 0.80 (s, 9H), 0.00 (s,

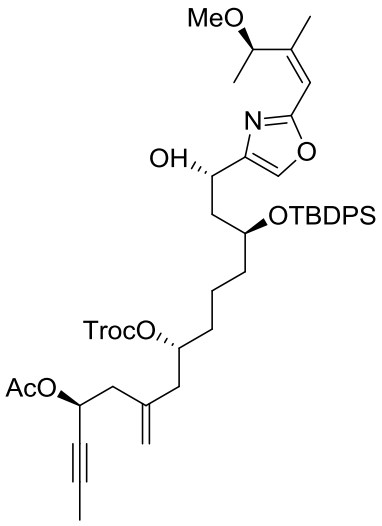
3H), −0.09 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.0, 159.8, 150.1, 144.7, 141.3, 135.90 (2C), 135.87 (2C), 134.6, 134.3, 133.5, 129.5, 129.4, 127.41 (2C), 127.39 (2C), 116.1, 113.5, 82.2, 76.5, 74.7, 70.4, 68.8, 65.6, 62.8, 56.4, 44.3, 44.0, 41.6, 37.2, 36.7, 27.1 (3C), 25.8 (3C), 21.0, 20.7, 19.4, 19.2, 18.1, 17.5, 17.5, 3.6, −4.5, −4.8; IR (film): $\tilde{\nu}$ = 3479, 2929, 2857, 1740, 1428, 1371, 1233, 1109, 837, 777, 703, 507 cm^{-1}; MS (ESI) *m*/*z* (%): 852 (*M*+Na$^+$, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{48}H_{71}NO_7Si_2Na$ [*M*+Na$^+$]: 852.4661, found: 852.4661.

(4*S*,8*R*,12*S*,14*S*)-14-((*tert*-Butyldimethylsilyl)oxy)-12-((*tert*-butyldiphenylsilyl)oxy)-14-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-6-methylene-8-(((2,2,2-trichloroethoxy)carbonyl)oxy) tetradec-2-yn-4-yl acetate (S9). 2,2,2-Trichlorethoxycarbonyl chloride (0.89 mL, 6.45 mmol) was added at 0 °C to a solution of alcohol **22** (1.79 g, 2.15 mmol), 4-(dimethylamino)pyridine (26.3 mg, 215 µmol, 0.10 equiv) and pyridine (1.04 mL, 12.9 mmol) in CH_2Cl_2 (20 mL). After stirring for 20 min at ambient temperature, the reaction was quenched with water (20 mL) and the aqueous phase was extracted with ethyl acetate (3 × 25 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated, and the residue was purified by flash chromatography (hexanes/ethyl acetate, 10:1) to give the title compound (2.15 g, quant.) as a colorless oil. $[\alpha]_D^{20}$ = −21.0 (c = 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.61 (m, 2H), 7.59 (m, 2H), 7.38 (m, 1H), 7.37 (m, 1H), 7.32 (m, 2H), 7.30 (m, 2H), 7.08 (d, *J* = 0.6 Hz, 1H), 6.14 (qd, *J* = 1.4, 1.0 Hz, 1H), 5.41 (tq, *J* = 6.9, 2.2 Hz, 1H), 5.18 (qd, *J* = 6.5, 0.7 Hz, 1H), 4.89 (dt, *J* = 1.3 Hz + not resolved, 1H), 4.88 (dt, *J* = 1.3 Hz + not resolved, 1H), 4.78 (t, *J* = 6.7 Hz, 1H), 4.75 (m, 1H), 4.74 (d, *J* = 11.9 Hz, 1H), 4.64 (d, *J* = 11.9 Hz, 1H), 3.84 (tt, *J* = 6.2, 5.4 Hz, 1H), 3.16 (s, 3H), 2.44 (d, *J* = 6.9 Hz, 2H), 2.26 (ddd, *J* = 14.6, 8.2, 0.7 Hz, 1H), 2.22 (ddd, *J* = 14.6, 5.0, 0.9 Hz, 1H), 2.02 (s, 3H), 2.00 (dt, *J* = 13.7, 6.7 Hz, 1H), 1.94 (dt, *J* = 13.7, 6.4 Hz, 1H), 1.87 (d, *J* = 1.4 Hz, 3H), 1.80 (d, *J* = 2.2 Hz, 3H), 1.46 (m, 1H), 1.39 (m, 1H), 1.36 (m, 1H), 1.29 (m, 2H), 1.25 (d, *J* = 6.5 Hz, 3H), 1.24 (m, 1H), 1.01 (s, 9H), 0.79 (s, 9H), 0.00 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.9, 159.8, 153.7, 150.2, 144.8, 139.4, 135.90 (2C), 135.84 (2C), 134.5, 134.2, 133.5, 129.5 (2C), 127.44 (2C), 127.43 (2C), 117.1, 113.5, 94.6, 82.1, 77.9, 76.53, 76.50, 74.7, 70.2, 65.6, 62.7, 56.4, 44.0, 41.4, 40.9, 36.4, 34.1, 27.1 (3C), 25.8 (3C), 21.0, 20.3, 19.4,

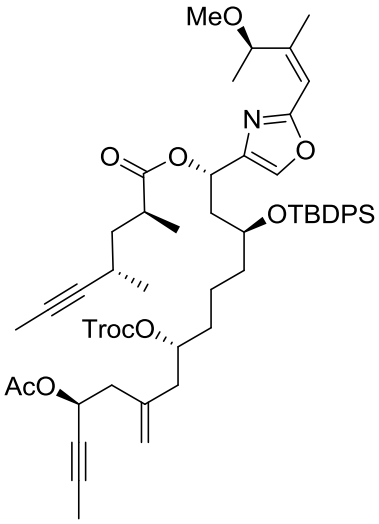


19.2, 18.1, 17.5, 3.6, −4.5, −4.9; IR (film): $\tilde{\nu}$ = 2954, 2930, 2857, 1755, 1378, 1250, 1110, 836, 821, 704, 507 cm^{-1}; MS (ESI) *m*/*z* (%): 1028 (*M*+Na^+, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{51}H_{72}NO_9Cl_3Si_2Na$ [*M*+Na^+]: 1026.3703, found: 1026.3703.

(4*S*,8*R*,12*S*,14*S*)-12-((*tert*-Butyldiphenylsilyl)oxy)-14-hydroxy-14-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-6-methylene-8-(((2,2,2-trichloroethoxy)carbonyl)oxy)tetradec-2-yn-4-yl acetate (23). 10-Camphorsulfonic acid (102 mg, 0.438 mmol, 10 mol%) was added to a solution of compound **S9** (2.20 g, 2.19 mmol) in CH_2Cl_2/MeOH (24 mL/8mL). After stirring for 8 h, TLC control indicated that the acetate started to get cleaved. At this point the mixture was neutralized with aq. sat. $NaHCO_3$ (40 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 25 mL) and the combined extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/ethyl acetate, 10:1 to 2:1) to give unreacted starting material (823 mg, 37%) and the desired product **23** (1.19 g, 61%, 98% brsm). $[\alpha]_D^{20}$ = −2.6 (c = 1.15, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.67 (m, 2H), 7.67 (m, 2H), 7.42 (m, 1H), 7.42 (m, 1H), 7.36 (m, 4H), 7.26 (d, *J* = 1.0 Hz, 1H), 6.15 (qd, *J* = 1.4, 1.0 Hz, 1H), 5.40 (tq, *J* = 6.9, 2.2 Hz, 1H), 5.10 (qd, *J* = 6.5, 0.8 Hz, 1H), 4.88 (dt, *J* = 1.3, 1.1 Hz, 1H), 4.86 (dt, *J* = 1.2 Hz + not resolved, 1H), 4.82 (dtd, *J* = 8.9, 3.8, 0.9 Hz, 1H), 4.72 (d, *J* = 11.9 Hz, 1H), 4.71 (m, 1H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.00 (tt, *J* = 7.2, 4.7 Hz, 1H), 3.18 (s, 3H), 3.06 (d, *J* = 3.8 Hz, 1H), 2.43 (dt, *J* = 6.9, 1.1 Hz, 2H), 2.25 (ddd, *J* = 14.5, 8.2, 0.6 Hz, 1H), 2.19 (ddd, *J* = 14.5, 4.8, 0.8 Hz, 1H), 2.02 (s, 3H), 1.99 (ddd, *J* = 14.2, 4.7, 3.9 Hz, 1H), 1.90 (ddd, *J* = 14.3, 8.8, 7.7 Hz, 1H), 1.86 (d, *J* = 1.4 Hz, 3H), 1.80 (d, *J* = 2.2 Hz, 3H), 1.45 (m, 1H), 1.33 (m, H), 1.31 (m, 1H) 1.27 (d, *J* = 6.5 Hz, 3H), 1.20 (m, 3H), 1.04 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.9, 160.4, 153.7, 150.5, 144.3, 139.3, 135.88 (2C), 135.87 (2C), 134.1, 133.5, 133.0, 129.9, 129.8, 127.7 (2C), 127.6 (2C), 117.1, 113.5, 94.6, 82.2, 77.7, 76.53, 76.46, 74.7, 72.8, 66.2, 62.7, 56.4, 42.6, 41.4, 40.9, 36.8, 33.9, 27.0 (3C), 21.0, 20.5, 19.29, 19.26, 17.6, 3.6; IR (film): $\tilde{\nu}$ = 3422, 2932, 2858, 1754, 1652, 1428, 1378, 1250, 1109, 1067, 1021, 821, 735, 704, 612, 508 cm^{-1}; MS (ESI) *m*/*z* (%): 914 (*M*+Na^+, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{45}H_{58}NO_9Cl_3SiNa$ [*M*+Na^+]: 912.2838, found: 912.2838.



(1*S*,3*S*,7*R*,11*S*)-11-Acetoxy-3-((*tert*-butyldiphenylsilyl)oxy)-1-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-9-methylene-7-(((2,2,2-trichloroethoxy)carbonyl)oxy)tetradec-12-yn-1-yl (2S,4S)-2,4-dimethylhept-5-ynoate (31).



2,4,6-Trichlorobenzoyl chloride (413 µL, 2.64 mmol)[13] and triethylamine (368 µL, 2.64 mmol) were added at 0 °C to a solution of acid **30** (299 mg, 1.94 mmol) in toluene (25 mL). The mixture was stirred at ambient temperature for 1 h. After cooling to 0 °C, a solution of alcohol **23** (1.57 g, 1.76 mmol) in toluene (20 mL) and 4-(dimethylamino)pyridine (215 mg, 1.76 mmol) were successively added. Stirring was continued for 1 h before the mixture was diluted with ethyl acetate (30 mL) and the reaction was quenched with hydrochloric acid (1 M, 80 mL). The aqueous phase was extracted with ethyl acetate (2 × 80 mL) and the combined extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/ethyl acetate, 10:1 to 4:1) to yield the title compound as a colorless syrup (1.81 g, quant.). $[\alpha]_D^{20}$ = −7.4 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64-7.57 (m, 4H), 7.44-7.29 (m, 6H), 7.19 (br s, 1H), 6.17-6.14 (m, 1H), 5.94-5.85 (m, 1H), 5.44 (ddq, J = 6.6, 1.8 Hz, 1H), 5.11 (qd, J = 6.6, 0.9 Hz, 1H), 4.91 (br s, 2H), 4.83-4.74 (m, 2H), 4.68 (d, *J* = 11.9 Hz, 1H), 3.68 (dt, *J* = 11.7, 5.6 Hz, 1H), 3.15 (s, 3H), 2.68-2.56 (m, 1H), 2.47 (d, *J* = 6.9 Hz, 2H), 2.36-2.08 (m, 5H), 2.05 (s, 3H), 1.88 (d, *J* = 1.3 Hz, 3H), 1.83 (d, *J* = 2.1 Hz, 3H), 1.74 (d, *J* = 2.3 Hz, 3H), 1.67 (ddd, *J* = 14.8, 9.7, 5.1 Hz, 1H), 1.54-1.30 (m, 7H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 170.1, 160.2, 153.9, 150.8, 140.1, 139.4, 136.03 (2C), 136.00 (2C), 135.2, 134.2, 134.0, 129.8 (2C), 127.6 (4C), 117.4, 113.4, 94.7, 83.0, 82.3, 77.9, 76.64, 76.57, 76.4, 74.8, 69.8, 65.7, 62.8, 56.6, 41.4, 41.2, 41.1, 39.6, 38.0, 36.4, 34.2, 27.1 (3C), 24.4, 21.8, 21.2, 20.5, 19.5, 19.3, 18.2, 17.8, 3.8, 3.7; IR (film): $\tilde{\nu}$ = 2962, 2932, 2858, 1753, 1737, 1448, 1428, 1377, 1249, 1162, 1110, 1064, 1021, 970, 821, 733, 704, 611, 507, 489 cm^{-1}; MS (ESI) *m*/*z* (%): 1050 (*M*+Na$^+$, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{54}H_{70}Cl_3NO_{10}SiNa$ [*M*+Na$^+$]: 1048.3727, found: 1048.3727.

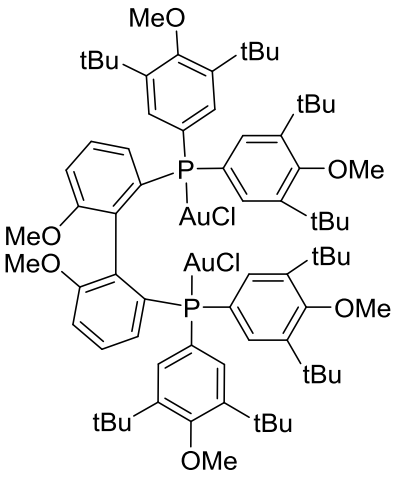
(3*S*,5*S*,8*S*,12*R*,16*S*,18*S*)-16-((*tert*-Butyldiphenylsilyl)oxy)-18-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-3,5-dimethyl-10-methylene-2-oxo-12-(((2,2,2-trichloroethoxy)carbonyl)oxy) oxacyclooctadec-6-yn-8-yl acetate (32). In a flame-dried 1 L two-neck round-bottom flask, molecular sieve 4 Å (8 g) and 5 Å (19 g) were added to a solution of diyne **31** (1.62 g, 1.57 mmol) in toluene (830 mL). After stirring for 1 h, a solution of complex **38** (640 mg, 0.483 mmol, 0.31 equiv)[14] was dissolved in an aliquot (20 mL) of the reaction mixture and added. The resulting suspension was stirred for 45 min at ambient temperature before it was filtered through a plug of Celite which was rinsed with *tert*-butyl methyl ether (100 mL). The combined filtrates were evaporated and the residue was purified by flash chromatography (hexanes/ethyl acetate, 15:1 to 4:1) to give cycloalkyne **32** as a colorless syrup (1.21 g, 79%). $[\alpha]_D^{20}$ = −1.5 (c = 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65-7.59 (m, 4H), 7.46-7.30 (m, 7H), 6.18-6.12 (m, 1H), 6.08 (dd, *J* = 9.3, 1.8 Hz, 1H), 5.46 (ddd, *J* = 9.0, 4.3, 1.4 Hz, 1H), 5.15 (qd, *J* = 6.4, 0.8 Hz, 1H), 4.96 (br s, 1H), 4.94 (d, *J* = 1.1 Hz, 1H), 4.84-4.66 (m, 3H), 3.91-3.77 (m, 1H), 3.19 (s, 3H), 2.63-2.18 (m, 7H), 2.06 (s, 3H), 1.95 (ddd, *J* = 15.0, 7.1, 2.2 Hz, 1H), 1.89 (d, *J* = 1.3 Hz, 4H), 1.69-1.39 (m, 5H), 1.38-1.30 (m, 2H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 169.9, 160.4, 153.9, 151.0, 140.9, 139.5, 135.9 (4C), 135.1, 134.11, 134.06, 129.8 (2C), 127.7 (4C), 116.9, 113.3, 94.7, 90.6, 78.2, 78.1, 76.6, 74.8, 70.2, 65.6, 63.4, 56.6, 41.9, 40.9, 40.7, 38.11, 38.09, 35.9, 34.1, 27.1 (3C), 24.1, 21.7, 21.3, 20.5, 19.4, 19.3, 17.8, 17.1; IR (film): $\tilde{\nu}$ = 2932, 2859, 1743, 1650, 1428, 1379, 1250, 1163, 1111, 1021, 821, 739, 704, 613, 570, 508 cm^{-1}; MS (ESI) *m*/*z* (%): 996 (*M*+Na$^+$, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{50}H_{64}Cl_3NO_{10}SiNa$ [*M*+Na$^+$]: 994.3257, found: 994.3257.

(3*S*,5*S*,8*S*,12*R*,16*S*,18*S*)-16-((*tert*-Butyldiphenylsilyl)oxy)-12-hydroxy-18-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-3,5-dimethyl-10-methylene-2-oxooxacyclooctadec-6-yn-8-yl acetate (33). Zinc dust (1.55 g, 23.6 mmol, Sigma-Aldrich®, < 10 μm) was added to a solution of compound **32** (230 mg, 0.236 mmol) in neat acetic acid (12 mL). The suspension was sonicated for 15 min. (if TLC showed

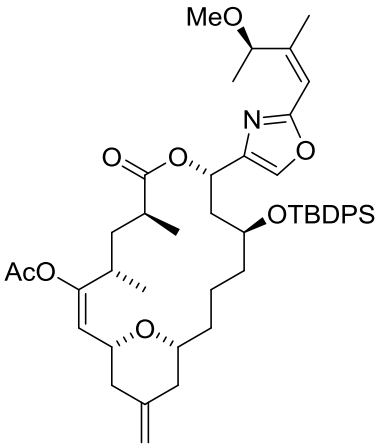
unconsumed starting material, the same amount of zinc dust was added and sonication was continued until full conversion was reached). The suspension was filtered through a plug of Celite which was rinsed with ethyl acetate (20 mL). The combined filtrates were diluted with toluene (10 mL) and all volatile materials were evaporated. The residue was purified by flash chromatography (hexanes/ethyl acetate, 4:1 to 2:1) to give the title compound (175 mg, 93%) as a pale yellow oil. $[\alpha]_D^{20}$ = −5.0 (c = 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (dd, *J* = 7.9, 1.3 Hz, 2H), 7.62 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.45-7.30 (m, 7H), 6.15 (dd, *J* = 1.5, 0.8 Hz, 1H), 6.06 (dd, *J* = 9.2, 1.8 Hz, 1H), 5.44 (ddd, *J* = 8.3, 4.8, 1.4 Hz, 1H), 5.15 (qd, *J* = 6.4, 0.8 Hz, 1H), 4.99 (br s, 1H), 4.97 (br s, 1H), 3.91-3.78 (m, 1H), 3.70-3.58 (m, 1H), 3.19 (s, 3H), 2.60 (q, *J* = 6.9 Hz, 1H), 2.56-2.38 (m, 4H), 2.32 (ddd, *J* = 14.9, 9.4, 2.6 Hz, 1H), 2.05 (s, 3H), 2.04-1.94 (m, 2H), 1.89 (d, *J* = 1.2 Hz, 3H), 1.72-1.52 (m, 4H), 1.51-1.42 (m, 1H), 1.42-1.30 (m, 4H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 169.8, 160.4, 150.9, 141.4, 140.9, 135.9 (4C), 134.2, 134.14, 134.13, 129.78, 129.77, 127.7 (4C), 116.8, 113.4, 90.5, 78.3, 74.8, 70.4, 68.8, 65.7, 63.7, 56.6, 45.0, 41.0, 40.6, 38.4, 38.0, 36.9, 35.9, 27.1, 24.0, 21.9, 21.3, 20.4, 19.4, 19.3, 17.8, 17.0; IR (film): $\tilde{\nu}$ = 3467, 2932, 2858, 1737, 1649, 1449, 1428, 1373, 1232, 1162, 1105, 1022, 969, 900, 856, 822, 757, 704, 612, 509, 489 cm^{-1}; MS (ESI) *m*/*z* (%): 820 (*M*+Na^+, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{47}H_{63}NO_8SiNa$ [*M*+Na^+]: 820.4215, found: 820.4215.

Compound 7-*epi*-33. Prepared analogously; it analyzed as follows: $[\alpha]_D^{20}$ = 25.0 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67-7.58 (m, 4H), 7.46-7.28 (m, 7H), 6.16-6.09 (m, 2H), 5.51 (ddd, *J* = 7.1, 4.8, 2.0 Hz, 1H), 5.16 (q, *J* = 6.4 Hz, 1H), 4.98 (br s, 1H), 4.96 (br s, 1H), 3.91-3.80 (m, 1H), 3.72-3.60 (m, 1H), 3.19 (s, 3H), 2.64-2.55 (m, 1H), 2.53-2.41 (m, 4H), 2.32 (ddd, *J* = 14.8, 9.6, 2.1 Hz, 1H), 2.12-2.03 (m, 1H), 2.07 (s, 3H), 1.94 (ddd, *J* = 15.0, 6.9, 2.1 Hz, 1H), 1.88 (d, *J* = 1.3 Hz, 3H), 1.84-1.71 (m, 1H), 1.66-1.56 (m, 2H), 1.55-1.41 (m, 2H), 1.38-1.29 (m, 3H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.25 (br s, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4, 170.0, 160.3, 150.8, 141.1, 141.0, 135.9 (4C), 134.2, 134.1 (2C), 129.8, 129.7, 127.6 (4C), 117.2, 113.4, 90.5, 78.2, 74.8, 70.7, 68.8, 65.5, 63.1, 56.6, 45.1, 41.4, 40.5, 38.2, 38.1, 36.9, 36.2, 27.1 (3C), 24.1, 22.4, 21.3, 20.4, 19.4, 19.3, 17.8, 17.2; IR (film): $\tilde{\nu}$ = 3478, 2931, 2858, 1739, 1648, 1451, 1428, 1373, 1233, 1164, 1109, 1026, 970, 902, 858, 822, 741, 704, 613, 509, 488 cm^{-1}; MS (ESI) *m*/*z* (%): 820 (*M*+Na^+, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{47}H_{63}NO_8SiNa$ [*M*+Na^+]: 820.4215, found: 820.4215.

Complex 39. A solution of chloro(dimethylsulfide)gold(I) (56.6 mg, 192 µmol) and (*R*) or (*S*)-3,5-*t*Bu-4-MeO-Biphep (111 mg, 96.1 µmol) in CH_2Cl_2 (7 mL) was stirred for 24 h at ambient temperature. The solvent was removed by a stream of argon and the colorless solid was dried on the high vacuum to obtain the title complex (quant.). The analytical data were in full agreement with those reported in literature.[15] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (td, *J* = 8.1, 2.5 Hz, 2H), 7.39 (d, *J* = 13.7 Hz, 4H), 7.11 (br d, *J* = 14.0 Hz, 4H), 7.02-6.86 (m, 4H), 3.72 (s, 6H), 3.69 (s, 6H), 2.72 (s, 6H), 1.33 (s, 72H); ^{31}P NMR (160 MHz, $CDCl_3$): δ = 21.9 (s).

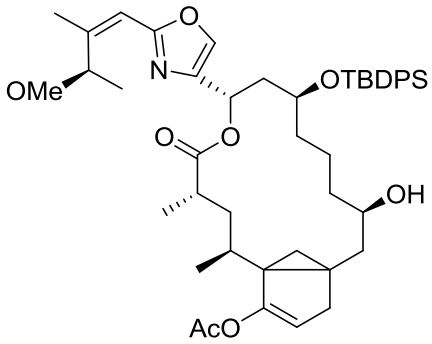


(1*R*,4*S*,6*S*,9*S*,11*S*,15*R*,*E*)-11-((*tert*-Butyldiphenylsilyl)oxy)-9-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-4,6-dimethyl-17-methylene-7-oxo-8,19-dioxabicyclo[13.3.1]nonadec-2-en-3-yl acetate (34). Silver hexafluoroantimonate (2.94 mg, 8.56 µmol, 0.34 equiv) and the gold complex (*R*)-**39** (6.89 mg, 4.26 µmol, 0.17 equiv) were suspended in CH_2Cl_2 (0.30 mL) and the mixture was sonicated for 5 min. The suspension was filtered through a plug of Celite (rinsing with CH_2Cl_2, 2 × 0.25 mL) into a solution of compound **33** (20.0 mg, 25.1 µmol) in CH_2Cl_2 (0.5 mL). After stirring for 48 h, the solvent was removed by a stream of argon and the residue was purified by flash chromatography (hexanes/ethyl acetate, 10:1) to give the title compound (18.1 mg, 91%) as a colorless oil. According to NMR, only the *E*-isomer has formed, which analyzed as follows: $[\alpha]_D^{20}$ = −28.9 (c = 0.98, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.70 (m, 2H), 7.64 (m, 2H), 7.40 (m, 1H), 7.37 (m, 1H), 7.34 (m, 2H), 7.32 (m, 2H), 7.15 (s, 1H), 6.08 (qd, *J* = 1.4, 1.0 Hz, 1H), 5.93 (dd, *J* = 12.4, 3.4 Hz, 1H), 5.11 (qd, *J* = 6.5, 0.7 Hz, 1H), 5.04 (d, *J* = 3.5 Hz, 1H), 4.69 (t, *J* = 1.8 Hz, 2H), 4.06 (ddd, *J* = 11.9, 3.5, 2.6 Hz, 1H), 3.74 (tdd, *J* = 10.2, 4.4, 1.8 Hz, 1H), 3.39 (tt, *J* = 11.3, 1.8 Hz, 1H), 3.14 (s, 3H), 2.57 (dqd, *J* = 8.9, 7.0, 6.0 Hz, 1H), 2.53 (dqd, *J* = 9.2, 6.9, 6.2 Hz, 1H), 2.33 (ddd, *J* = 13.9, 12.4, 4.4 Hz, 1H), 2.27 (ddd, *J* = 13.4, 2.5, 1.4 Hz, 1H), 2.09 (s, 3H), 2.08 (ddtd, *J* = 13.4, 11.9, 1.6, 0.9, 1H), 2.08 (m,1H), 1.94 (ddtd, *J* = 13.3,



11.3, 1.6, 1.0 Hz, 1H), 1.87 (ddd, *J* = 13.9, 10.1, 3.5 Hz, 1H), 1.84 (d, *J* = 1.6 Hz, 3H), 1.83 (m, 1H), 1.72 (t, *J* = 13.1 Hz, 1H), 1.67 (m, 1H), 1.33 (m, 2H), 1.25 (m, 1H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.16 (dd, *J* = 9.1, 6.1 Hz, 2H), 1.03 (s, 9H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.69 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.0, 169.3, 160.1, 154.7, 151.0, 144.2, 141.0, 136.1 (2C), 135.9 (2C), 134.9, 133.8, 133.4, 129.7, 129.5, 127.7 (2C), 127.4 (2C), 119.9, 113.0, 109.1, 74.7, 74.6, 72.8, 71.7, 64.9, 56.5, 41.4, 40.95, 40.94, 40.0, 37.7, 34.5, 34.3, 32.8, 27.1 (3C), 22.0, 21.0, 20.0, 19.4, 19.0, 18.1, 17.6; IR (film): $\tilde{\nu}$ = 2934, 2858, 1759, 1733, 1653, 1456, 1428, 1367, 1258, 1194, 1163, 1106, 1056, 1024, 899, 821, 743, 704, 610, 511, 491, 451 cm^{-1}; MS (ESI) *m*/*z* (%): 820 (*M*+Na$^+$, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{47}H_{63}NO_8SiNa$ [*M*+Na$^+$]: 820.4215, found: 820.4215.

(1*S*,3*S*,6*S*,8*S*,12*R*)-8-((*tert*-Butyldiphenylsilyl)oxy)-12-hydroxy-6-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-1,3-dimethyl-4-oxo-1,2,3,4,6,7,8,9,10,11,12,13-dodecahydro-14H-13a,16a-methanocyclopenta[f][1]oxacyclopentadecin-16-yl acetate (40). The reaction was performed analogously, using (*S*)-**39** as precatalyst. Flash chromatography (hexanes/ethyl acetate, 10:1) gave product **34** (50-70%) as an inseparable mixture of the *E* and *Z* isomers (~ 4:1) and product **40** (20-30%), which analyzed as follows: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.59 (m, 2H), 7.57 (m, 2H), 7.38 (m, 1H), 7.36 (m, 1H), 7.31 (m, 2H), 7.28 (m, 2H), 7.24 (s, 1H), 6.09 (qd, *J* = 1.4, 1.0 Hz, 1H), 6.07 (dd, *J* = 9.2, 2.4 Hz, 1H), 5.13 (t, *J* = 2.5 Hz, 1H), 5.06 (qd, *J* = 6.4, 0.8 Hz, 1H), 3.86 (dddd, *J* = 8.0, 6.9, 5.7, 2.3 Hz, 1H), 3.60 (m, 1H), 3.12 (s, 3H), 2.62 (dd, *J* = 17.5, 2.7 Hz, 1H), 2.41 (dd, *J* = 17.5, 2.2 Hz, 1H), 2.39 (dqi, *J* = 7.0, 6.7 Hz,1H), 2.21 (ddd, *J* = 15.1, 9.2, 2.4 Hz, 1H), 2.10 (s, 3H), 1.91 (ddd, *J* = 15.1, 8.0, 2.5 Hz, 1H), 1.85 (d, *J* = 1.4 Hz, 3H), 1.78 (m, 1H), 1.72 (m, 1H) 1.66 (dd, *J* = 14.4, 3.1 Hz, 1H), 1.54 (m, 1H), 1.52 (ddd, *J* = 14.4, 10.2, 1.1, 1H), 1.45 (m, 2H), 1.42 (m, 1H), 1.39 (m, 1H), 1.35 (m, 1H), 1.25 (d, *J* = 6.5 Hz, 3H), 1.21 (m, 1H), 1.05 (d, *J* = 7.0 Hz, 3H), 1.04 (m, 1H), 1.02 (s, 9H), 0.93 (d, *J* = 7.1 Hz, 3H), 0.60 (dd, *J* = 4.0, 0.8 Hz, 1H), 0.41 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 176.0, 168.3, 160.1, 153.7, 150.6, 140.4, 135.8 (2C), 135.7 (2C), 134.3, 134.2 (2C), 129.6 (2C), 127.49 (2C), 127.48 (2C), 113.2, 110.5, 74.7, 73.3, 70.7, 65.2, 56.4, 40.9, 40.5, 39.8, 38.7, 37.6, 36.8, 36.6, 36.5, 31.0, 29.6, 27.0 (3C), 24.1, 21.3, 20.7, 20.4, 19.3, 19.2, 18.1, 17.6.

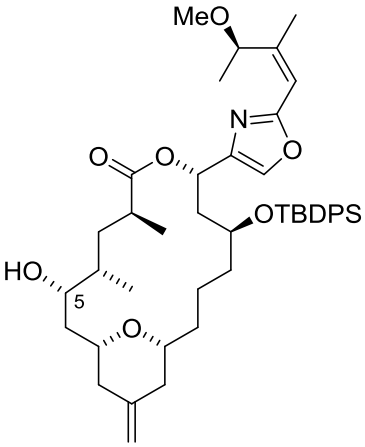


(2*S*,4*S*,7*S*,9*S*,13*R*)-9-((*tert*-Butyldiphenylsilyl)oxy)-13-hydroxy-7-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-2,4-dimethyl-6-oxa-1(1,3)-benzenacyclotetradecaphan-5-one (41). Prepared analogously starting with 7-*epi*-**33**, using (*R*)-**39** as the precatalyst. The crude product was purified by preparative LC (Kromasil 100-5C18 5µm, 150 mm × 21.2 mm, MeCN/H_2O, 95:5, 35 °C, 20 mL/min) to give **34** (10-20%) as an inseparable mixture of the *E* and *Z* isomers (~4:1) and compound **41** (~50%), which analyzed as follows: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.61 (m, 2H), 7.60 (m, 2H), 7.42 (s, 1H), 7.39 (m, 1H), 7.38 (m, 1H), 7.32 (m, 4H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 1.7, 1H), 7.08 (ddd, *J* = 7.5, 1.3, 1.3 Hz, 1H), 7.06 (ddd, , *J* = 7.4, 2.9 Hz, 1H), 6.17 (dd, *J* = 10.8, 2.4 Hz, 1H), 6.14 (qd, *J* = 1.4, 0.9 Hz, 1H), 5.25 (qd, *J* = 6.4, 0.5 Hz, 1H), 3.94 (dddd, *J* = 10.3, 6.5, 4.8, 1.2 Hz, 1H), 3.83 (br s, 1H), 3.19 (s, 3H), 2.89 (dd, *J* = 13.9, 4.4 Hz, 1H), 2.81 (dd, *J* = 13.9, 2.8 Hz, 1H), 2.61 (dqd, *J* = 12.2, 7.0, 3.1 Hz, 1H), 2.56 (ddd, *J* = 15.2, 10.8, 1.2 Hz, 1H), 2.10 (dqd, *J* = 11.4, 6.9, 2.5 Hz, 1H), 1.85 (d, *J* = 1.5 Hz, 3H), 1.80 (ddd, *J* = 15.2, 6.5, 2.5 Hz, 1H), 1.74 (ddd, *J* = 13.8, 11.4, 3.1 Hz, 1H), 1.59 (m, 1H), 1.51 (m, 1H), 1.44 (m, 1H), 1.42 (m, 1H), 1.34 (br s, 1H), 1.24 (m, 1H), 1.19 (d, *J* = 6.5 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.03 (s, 9H), 1.01 (m, 2H), 1.00 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 176.7, 160.2, 150.7, 146.4, 140.8, 135.78 (2C), 135.77 (2C), 135.4, 134.4, 134.2, 134.1, 132.3, 129.7, 129.6, 128.7, 128.0, 127.6 (2C), 127.5 (2C), 122.9, 113.2, 74.7, 71.1, 70.7, 65.3, 56.5, 45.6, 39.9, 37.4, 37.1, 36.8, 36.0, 35.6, 27.0 (3C), 22.5, 22.2, 19.3, 19.2, 18.3, 17.6.

(1*R*,4*S*,6*S*,9*S*,11*S*,15*R*)-11-((*tert*-Butyldiphenylsilyl)oxy)-9-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-4,6-dimethyl-17-methylene-8,19-dioxabicyclo[13.3.1]nonadecane-3,7-dione (35). Potassium carbonate (32.7 mg, 237 µmol) was added to a solution of compound **34** (63.0 mg, 78.9 µmol) in methanol (10 mL). After stirring 3 h, the mixture was filtered through a plug of Celite which was rinsed with *tert*-butyl methyl ether (10 mL). The combined filtrates were concentrated and the residue was purified by flash chromatography (hexanes/ethyl acetate, 10:1) to give the title compound (56.8 mg, 95%) as a colorless oil. $[\alpha]_D^{20}$ = −28.6 (c = 1.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (dd, *J* = 7.9, 1.4 Hz,

2H), 7.64 (dd, *J* = 7.9, 1.4 Hz, 2H), 7.46-7.30 (m, 6H), 7.21 (d, *J* = 0.8 Hz, 1H), 6.12 (qd, *J* = 1.4, 0.8 Hz, 1H), 5.95 (dd, *J* = 11.4, 2.8 Hz, 1H), 5.14 (qd, *J* = 6.4, 0.8 Hz, 1H), 4.75-4.68 (m, 2H), 3.76- 3.62 (m, 1H), 3.54 (dd, *J* = 10.4 Hz, 1H), 3.39 (dd, *J* = 10.4 Hz, 1H), 3.16 (s, 3H), 2.81 (dd, *J* = 15.4, 9.9 Hz, 1H), 2.70-2.61 (m, 1H), 2.41-2.25 (m, 2H), 2.25-2.06 (m, 3H), 2.01-1.90 (m, 3H), 1.87 (d, *J* = 1.4 Hz, 3H), 1.80-1.71 (m, 3H), 1.41-1.30 (m, 5H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.05 (s, 9H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.9, 175.0, 160.3, 151.1, 144.0, 141.1, 136.2 (2C), 136.0 (2C), 134.7, 133.8, 133.7, 129.9, 129.7, 127.8 (2C), 127.6 (2C), 113.2, 109.4, 75.2, 74.8, 74.3, 71.4, 65.0, 56.6, 48.5, 42.9, 41.4, 40.8, 40.5, 39.0, 36.0, 35.0, 33.9, 27.2 (3C), 20.8, 19.6, 19.3, 18.8, 17.8, 17.7; IR (film): $\tilde{\nu}$ = 2932, 2857, 1729, 1703, 1652, 1456, 1428, 1380, 1259, 1163, 1103, 1058, 892, 821, 804, 755, 702, 611, 509, 488 cm^{-1}; MS (ESI) *m*/*z* (%): 778 (*M*+Na$^+$, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{45}H_{61}NO_7SiNa$ [*M*+Na$^+$]: 778.4110, found: 778.4110.

(1*R*,3*S*,4*S*,6*S*,9*S*,11*S*,15*R*)-11-((*tert*-Butyldiphenylsilyl)oxy)-3-hydroxy-9-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-4,6-dimethyl-17-methylene-8,19-dioxabicyclo[13.3.1]nonadecan-7-one (36).



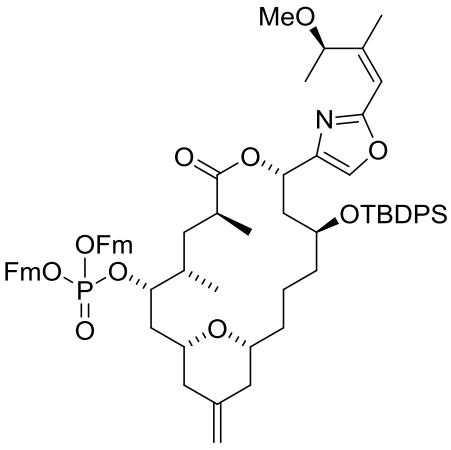
Sodium borohydride (12.5 mg, 331 µmol) was added at –40 °C to a solution of ketone **35** (50.0 mg, 66.1 µmol) in MeOH (5 mL). After stirring for 3 h at this temperature, excess reagent was quenched with aq. phosphate buffer (pH 7, 10 mL) and the solution was allowed to reach ambient temperature. The aqueous phase was extracted with *tert*-butyl methyl ether (3 x 10 mL) and the combined extracts were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 8:1 to 2:1) to yield **36** (30.8 mg, 61%) and 5-*epi*-**36** (16.4 mg, 33%), each as a colorless oil.

Analytical data of compound **36**: $[\alpha]_D^{20}$ = −31.4 (c = 1.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.67 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.45-7.32 (m, 6H), 7.28 (d, *J* = 0.6 Hz, 1H), 6.14-6.11 (m, 1H), 5.72 (dd, *J* = 11.9, 3.3 Hz, 1H), 5.12 (qd, *J* = 6.5, 0.9 Hz, 1H), 4.70-4.64 (m, 2H), 3.85-3.66 (m, 2H), 3.35-3.19 (m, 2H), 3.17 (s, 3H), 2.52 (dqd, *J* = 10.3, 7.0, 3.6 Hz, 1H), 2.41 (ddd, *J* = 14.0, 12.1, 3.9 Hz, 1H), 2.13 (br s, 1H), 2.09 (br s, 1H), 2.01-1.88 (m, 4H), 1.87 (d, *J* = 1.4 Hz, 3H), 1.77-1.50 (m, 7H),1.48-1.30 (m, 4H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.05 (s, 9H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.71 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8, 160.2, 151.1, 145.0, 140.8, 136.2 (2C), 136.0 (2C),

134.7, 134.3, 134.0, 129.8, 129.6, 127.8 (2C), 127.6 (2C), 113.3, 108.5, 77.2, 76.0, 75.2, 74.9, 71.2, 68.7, 65.9, 56.6, 41.9, 41.7, 41.4, 41.0, 37.9, 36.3, 35.6, 33.8, 33.6, 27.3 (3C), 21.4, 19.6, 19.2, 17.7, 16.5, 13.5; IR (film): $\tilde{\nu}$ = 3468, 2933, 2857, 1726, 1652, 1549, 1454, 1428, 1380, 1248, 1204, 1150, 1103, 1044, 1005, 976, 955, 891, 822, 756, 703, 611, 510, 488 cm^{-1}; MS (ESI) *m*/*z* (%): 780 (*M*+Na^+, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{45}H_{63}NO_7SiNa$ [*M*+Na^+]: 780.4266, found: 780.4266.

Analytical data of compound 5-*epi*-**36**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.66 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.46-7.33 (m, 6H), 7.25 (d, *J* = 0.6 Hz, 1H), 6.14-6.11 (m, 1H), 5.84 (dd, *J* = 11.3, 3.2 Hz, 1H), 5.10 (qd, *J* = 6.4, 0.8 Hz, 1H), 4.69 (br s, 2H), 3.8-3.75 (m, 1H), 3.57-3.24 (m, 4H), 3.17 (s, 3H), 2.92-2.81 (m, 1H), 2.32 (ddd, *J* = 14.5, 11.4, 3.4 Hz, 1H), 2.13 (br d, *J* = 13.0 Hz, 1H), 2.10 (br d, *J* = 11.9 Hz, 1H), 2.04-1.88 (m, 3H), 1.86 (d, *J* = 1.4 Hz, 3H), 1.79-1.29 (m, 11H), 1.25 (d, *J* = 6.4 Hz, 3H), 1.03 (s, 9H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 160.3, 151.1, 144.9, 141.0, 136.1 (2C), 136.0 (2C), 134.7, 134.0 (2C), 129.8, 129.6, 127.8 (2C), 127.6 (2C), 113.3, 108.6, 76.0, 75.5, 75.2, 74.9, 71.3, 65.8, 56.6, 41.9, 41.5, 40.9, 40.4, 40.2, 39.2, 35.7, 35.0, 33.9, 27.2 (2C), 21.4, 19.6, 19.2, 18.0, 17.8, 17.2.

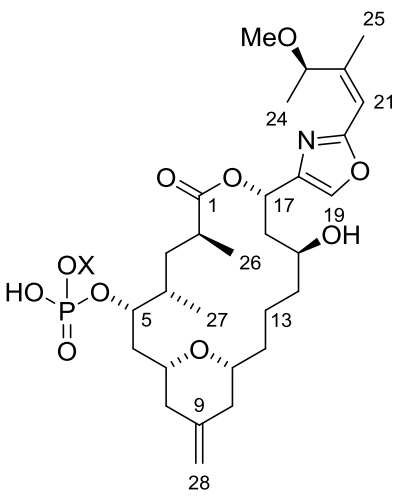
Bis-((9*H*-fluoren-9-yl)methyl) ((1*R*,3*S*,4*S*,6*S*,9*S*,11*S*,15*R*)-11-((*tert*-butyldiphenylsilyl)-oxy)-9-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol -4-yl)-4,6-dimethyl-17-methylene-7-oxo-8,19-dioxa bicyclo[13.3.1]nonadecan-3-yl) phosphate (37). A solution of



a tetrazole (0.45 M in MeCN, 264 µL, 119 µmol) was added at 0 °C to a solution of alcohol **36** (30.0 mg, 39.6 µmol) and *i*$Pr_2NP(OFm)_2$ (62.9 mg, 119 µmol)[22] in MeCN (0.75 mL) and CH_2Cl_2 (0.75 mL). The mixture was stirred for 3 h at ambient temperature before it was cooled to 0 °C and aq. hydrogen peroxide (35% *w*/*w*, 115 µL, 1.19 mmol) was added. After stirring for additional 30 min, the reaction was quenched with aq. sat. $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/ethyl acetate, 6:1 to 2:1) to afford the title compound (47.1 mg, quant.) as a colorless solid. $[\alpha]_D^{20}$ = −11.1 (c = 2.35, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.69 (m, 3H), 7.63 (m, 2H), 7.52 (d, *J* = 7.5 Hz, 2H), 7.50 (d, *J*

= 7.5 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H),7.39-7.33 (m, 10H), 7.27 (td, *J* = 7.5, 1.0 Hz, 1H), 7.26 (td, *J* = 7.4, 1.1 Hz, 1H), 7.25 (td, *J* = 7.4, 1.1 Hz, 1H), 7.21 (td, *J* = 7.5, 1.1 Hz, 1H), 7.15 (s, 1H), 6.08 (s, 1H), 5.79 (dd, *J* = 12.5, 2.9 Hz, 1H), 5.11 (q, *J* = 6.5 Hz, 1H), 4.68 (m, 2H), 4.51 (dddd, *J* = 11.6, 6.8, 4.8, 1.0 Hz, 1H), 4.23-4.14 (m, 4H), 4.10 (m, 2H), 3.59 (m, 1H), 3.23 (tt, *J* = 11.1, 2.0 Hz, 1H), 3.14 (s, 3H), 2.98 (ddd, *J* = 11.4, 9.1, 2.3 Hz, 1H), 2.55 (dqd, *J* = 12.7, 6.7, 4.0 Hz, 1H), 2.26 (ddd, *J* = 13.7, 12.5, 4.0 Hz, 1H), 2.07 (d, *J* = 13.3 Hz, 1H), 1.97 (d, *J* = 13.1 Hz, 1H), 1.84 (m, 1H), 1.84 (d, *J* = 1.5 Hz, 3H), 1.84 (m, 1H), 1.83 (m, 1H), 1.82 (m, 1H), 1.80 (m, 1H), 1.64 (dd, *J* = 14.0, 4.7 Hz, 1H), 1.63 (ddd, *J* = 12.4, 9.6, 1.6 Hz, 1H), 1.58 (m, 1H), 1.40 (m, 1H), 1.30 (m, 2H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.21 (m, 1H), 1.20 (m, 1H), 1.02 (s, 9H), 0.83 (td, *J* = 13.3, 3.0 Hz, 1H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.60 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.0, 160.1, 151.0, 144.5, 143.15, 143.13, 143.12, 143.05, 141.34 (3C), 141.31, 141.2, 136.1 (2C), 135.9 (2C), 134.8, 133.6, 133.3, 129.7, 129.5, 127.90, 127.87 (2C), 127.84, 127.7 (2C), 127.4 (2C), 127.14, 127.12, 127.11, 127.07, 125.2, 125.03, 125.00 (2C), 120.09, 120.03, 120.02, 120.00, 113.0, 108.6, 78.5 (d, $J_{C\text{-}P}$ = 7.0 Hz), 74.72, 74.69, 74.3, 71.3, 69.2 (d, $J_{C\text{-}P}$ = 5.9 Hz), 68.9 (d, $J_{C\text{-}P}$ = 6.1 Hz), 64.9, 56.5, 48.0 (d, $J_{C\text{-}P}$ = 5.4 Hz), 47.9 (d, $J_{C\text{-}P}$ = 5.8 Hz), 41.7, 41.5, 41.2, 38.6, 37.9, 37.5, 35.1, 33.3, 33.2 (d, $J_{C\text{-}P}$ = 6.6 Hz), 27.1 (3C), 21.1, 19.5, 19.0, 17.6, 17.4, 13.7; ^{31}P NMR (160 MHz, $CDCl_3$): δ = 0.00 (s); IR (film): $\tilde{\nu}$ = 3069, 2934, 2892, 2857, 1727, 1450, 1428, 1381, 1261, 1205, 1150, 1105, 1045, 1003, 988, 914, 823, 757, 740, 704, 612, 511, 494 cm^{-1}; MS (ESI) *m*/*z* (%): 1217 (*M*+Na$^+$, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{73}H_{84}NO_{10}PSiNa$ [*M*+Na$^+$]: 1216.5494, found: 1216.5494.

Enigmazole A (1). A solution of tetrabutylammonium fluoride (1 M in THF, 188 µL, 188 µmol) was added to a solution of compound **37** (4.50 mg, 3.77 µmol) in THF (0.5 mL) and acetic acid (16.2 µL, 283 µmol,) and the resulting mixture was stirred at 40 °C for 9 d. After reaching ambient temperature, the solution was diluted with water (1 mL) and loaded onto a C18-cartridge (Strata® C18-U, 55 µm, 70 Å, 500 mg/6 mL). The salts were eluted with water, followed by elution of the organic fraction with MeOH. The combined organic fractions was concentrated and the residue purified by preparative LC (Kromasil 100-5C18 5µm, 150 mm × 21.2 mm, MeOH/aq. TEAA pH 8.0, 70:30 to 100% MeOH over 10 min, 35 °C, 20 mL/min) to obtain the



tetrabutylammonium salt of enigmazole A (2.60 mg, 82%) as a colorless powder after lyophilisation.

Purification by preparative LC (amount < 0.5 mg, Kromasil 100-5C18 5µm, 150 mm × 21.2 mm, MeCN/aq. TEAA pH 8.0, 30:70 to 50:50 over 6 min, 35 °C, 20 mL/min) afforded the triethylammonium salt of Enigmazole A (quant.) after lyophilisation.

The protonated form of Enigmazole A was obtained by ion exchange chromatography (Adsorbex® SCX 400 mg) using MeOH as eluent.

Analytical data of the triethylammonium salt: for the ^{1}H and ^{13}C NMR data, see Tables S1 and S2; $[\alpha]_D^{20}$ = −9.7 (c = 0.50, $CHCl_3$); ^{31}P NMR (160 MHz, $CDCl_3$): δ = 0.00 (s); IR (film): $\tilde{\nu}$ = 3402 (br), 2977, 2935, 2854, 1726, 1651, 1455, 1252, 1203, 1150, 1109, 1076, 1017, 972, 936, 896, 657, 594, 515, 497 cm^{-1}; MS (ESI) *m*/*z* (%): 598 (*M*−H$^-$, 100); HRMS (ESI): *m*/*z*: calcd. for $C_{29}H_{45}NO_{10}P$ [*M*−H$^-$]: 598.2787, found: 598.2787;

Analytical data of the free acid: for the ^{1}H and ^{13}C NMR data, see Tables S1 and S2; ^{31}P NMR (160 MHz, $CDCl_3$): δ = 0.00 (s).

Table S1: Comparison of ^{1}H NMR data (CD_3OD) of Enigmazole A;

numbering scheme as shown in the Insert

Position	Natural product,[16] free acid	Molinski Group,[17] Na-salt	this work, Et_3NH-salt	this work, free acid
9	7.68, s	7.69, s	7.68, d, 0.5	7.68, d, 0.4
21	6.21, s	6.22, br s	6.21, qd, 1.4, 1.0	6.20, qd, 1.4, 1.0
17	5.95, dd, 12.8, 2.5	5.96, dd, 12.5, 2.5	5.95, ddd, 12.8, 2.8, 0.5	5.95, ddd, 12.8, 2.9, 0.4
23	5.24, q, 6.5	5.25, q, 6.3	5.24, qd, 6.5, 0.9	5.23, qd, 6.5, 0.9
28a	4.70, d, 1.5	4.71, br s	4.70, q, 2.0	4.70, q, 1.9
28b	4.69, d, 1.5	4.70, br s	4.69, q, 2.0	4.69, q, 1.9
5	4.42, m	4.43, m	4.42, dddd, 11.2, 8.8, 4.4, 1.0	4.47, m
15	3.62, dt, 11.1, 4.3	3.63, m	3.60, tdd, 10.8, 4.1, 1.8	3.60, tdd, 10.8, 4.1, 1.8
11	3.29	3.30	3.30, tt, 11.0, 2.4	3.29, tt, 11.1, 2.4
23-OMe	3.20, s	3.21, s	3.20, s	3.19, s
Et_3NH	-	-	3.17, q, 7.3	-
7	3.12, dd, 10.3, 9.8	3.13, m	3.12, ddd, 11.4, 8.6, 2.3	3.12, ddd, 11.4, 8.6, 2.0
2	2.98	2.99, m	2.98, dqd, 12.5, 6.7, 3.8	2.95, m
16a	2.50, dt, 13.2, 3.4	2.51, dt, 13.3, 3.8	2.50, ddd, 13.8, 12.8, 4.1	2.50, ddd, 13.8, 12.8, 4.1
8a	2.21, d, 12.8	2.23, d, 13.0	2.21, ddd, 13.0, 2.3, 1.2	2.20, br d, 13.2
10a	2.13, d, 12.8	2.14, d, 14.0	2.13, ddd, 13.1, 2.4, 1.2	2.13, br d, 13.2
6a	2.10, m	2.11, m	2.09, dd, 14.4, 4.4	2.07, br d, 14.4
8b	1.97, dd, 12.8, 12.3	1.98, t, 12.3	1.97, ddtd, 13.0, 11.4, 1.7, 1.0	1.97, m
25	1.89, s	1.89, d, 1.5	1.88, d, 1.6	1.88, d, 1.5
3a	1.88, m	1.89, m	1.88, m	1.87, m
6b	1.87, m	1.88, m	1.87, m	1.90, m
10b	1.84	1.86	1.85, m	1.84, m
14a	1.76	1.79	1.78, m	1.78, tt, 12.9, 1.9
16b	1.77	1.78	1.77, ddd, 13.8, 10.8, 2.9	1.77, ddd, 13.8, 10.8, 2.9
13a	1.72	1.73	1.72, m	1.72, tq, 13.0, 3.8
12a	1.64	1.66	1.65, m	1.64, dddd, 14.0, 11.2, 3.8, 2.8
4	1.62	1.63	1.64, m	1.64, m
13b	1.54, q, 12.4	1.55, q, 12.5	1.53, tdt, 13.0, 12.6, 2.9	1.52, tdt, 13.0, 12.7, 2.8
3b	1.38, t, 10.8	1.39, m	1.40, m	1.41, td, 13.2, 2.5
12b	1.37, t, 11.3	1.38, m	1.38, m	1.37, dddd, 14.0, 13.2, 3.3, 2.4
Et_3NH	-	-	1.30, t, 7.3	-
24	1.26, d, 6.4	1.27, d, 6.5	1.26, d, 6.5	1.26, d, 6.5
26	1.10, d, 6.4	1.11, d, 6.5	1.10, d, 6.7	1.10, d, 6.6
14b	1.02, td, 12.0, 3.4	1.04, dt, 12.0, 3.2	1.02, m	1.02, tdd, 12.8, 11.2, 4.1
27	0.97, d, 6.4	0.98, d, 6.5	0.97, d, 6.6	0.97, d, 6.5

Table S2: Comparison of ^{13}C NMR data (CD_3OD) of Enigmazole A;

numbering scheme as shown in the Insert

Position	Natural product,[16] free acid	Molinski Group,[17] Na-salt	this work, Et_3NH-salt	this work, protonated
1	176.4	176.5	176.5	176.5
20	161.7	161.9	161.9	161.9
22	152.7	152.7	152.7	152.7
9	146.3	146.6	146.6	146.5
18	142.3	142.4	142.4	142.3
19	136.0	135.9	135.9	135.9
21	113.9	114.0	114.0	114.0
28	108.8	108.6	108.7	108.7
7	77.2	77.6	77.5	77.4
23	77.0	76.2	76.2	76.2
11	76.2	75.7	75.8	75.9
5	75.8	75.2, d, 6.1	75.4,d ,6.3	75.8, br
15	69.8	69.8	69.8	69.8
17	65.9	65.6	65.7	65.8
23-OMe	56.8	56.8	56.8	56.8
Et_3NH	-	-	47.6	-
8	43.0	43.0	43.1	43.1
16	42.6	42.7	42.7	42.6
10	42.4	42.5	42.5	42.5
6	40.1	40.1	40.2	40.1
2	39.6	39.7	39.7	39.7
3	39.3	39.3	39.4	39.3
4	36.2	34.7, d, 6.1	34.7, d, 6.4	34.7 d, 4.6
12	36.2	36.2	36.2	36.2
14	33.6	33.6	33.6	33.6
13	21.8	21.8	21.8	21.8
24	19.4	19.4	19.4	19.4
26	18.2	18.3	18.3	18.3
25	17.6	17.7	17.7	17.7
27	14.7	15.0	15.0	14.9
Et_3NH	-	-	9.2	-

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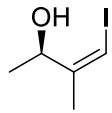
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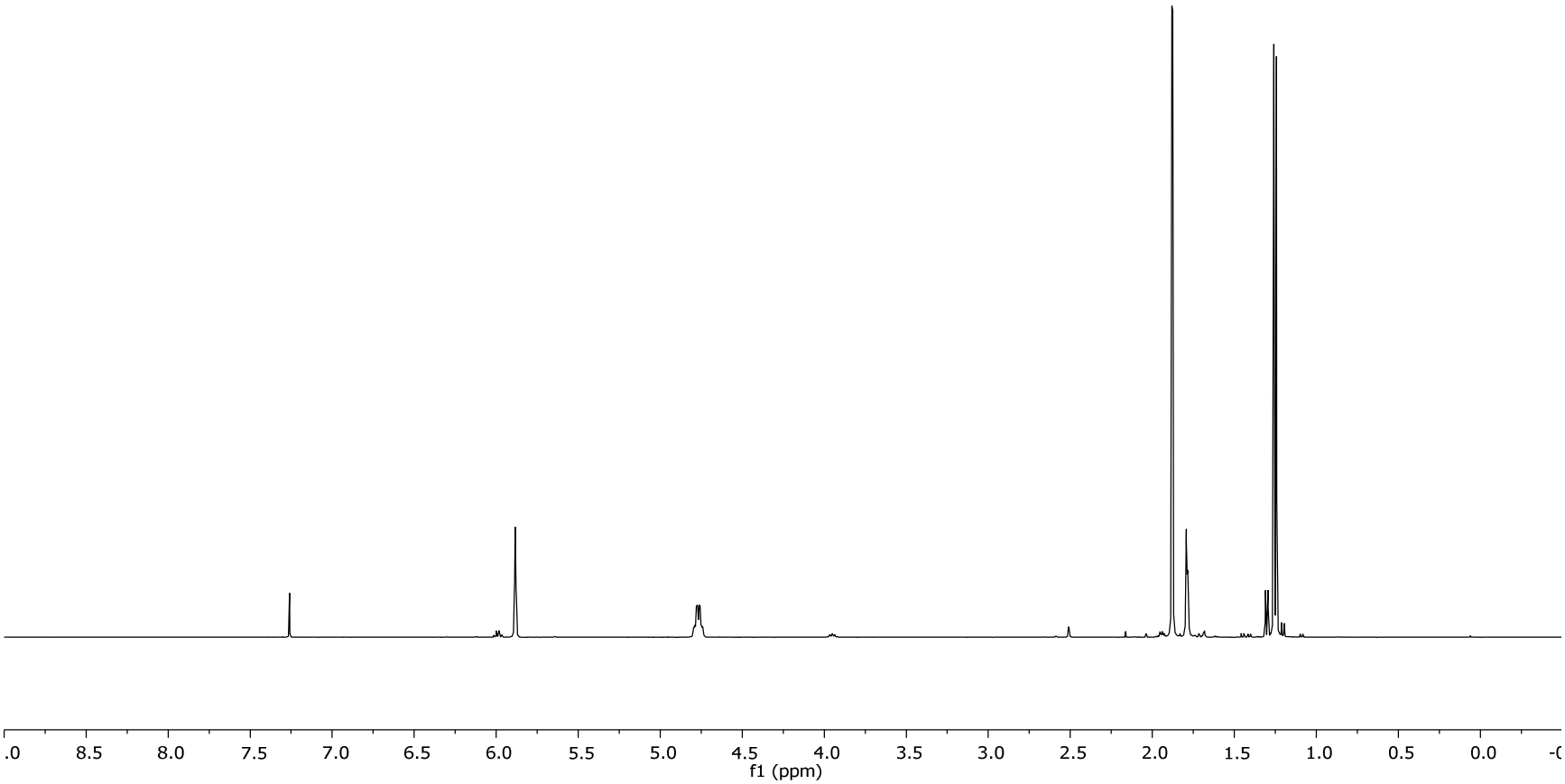
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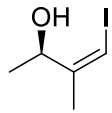
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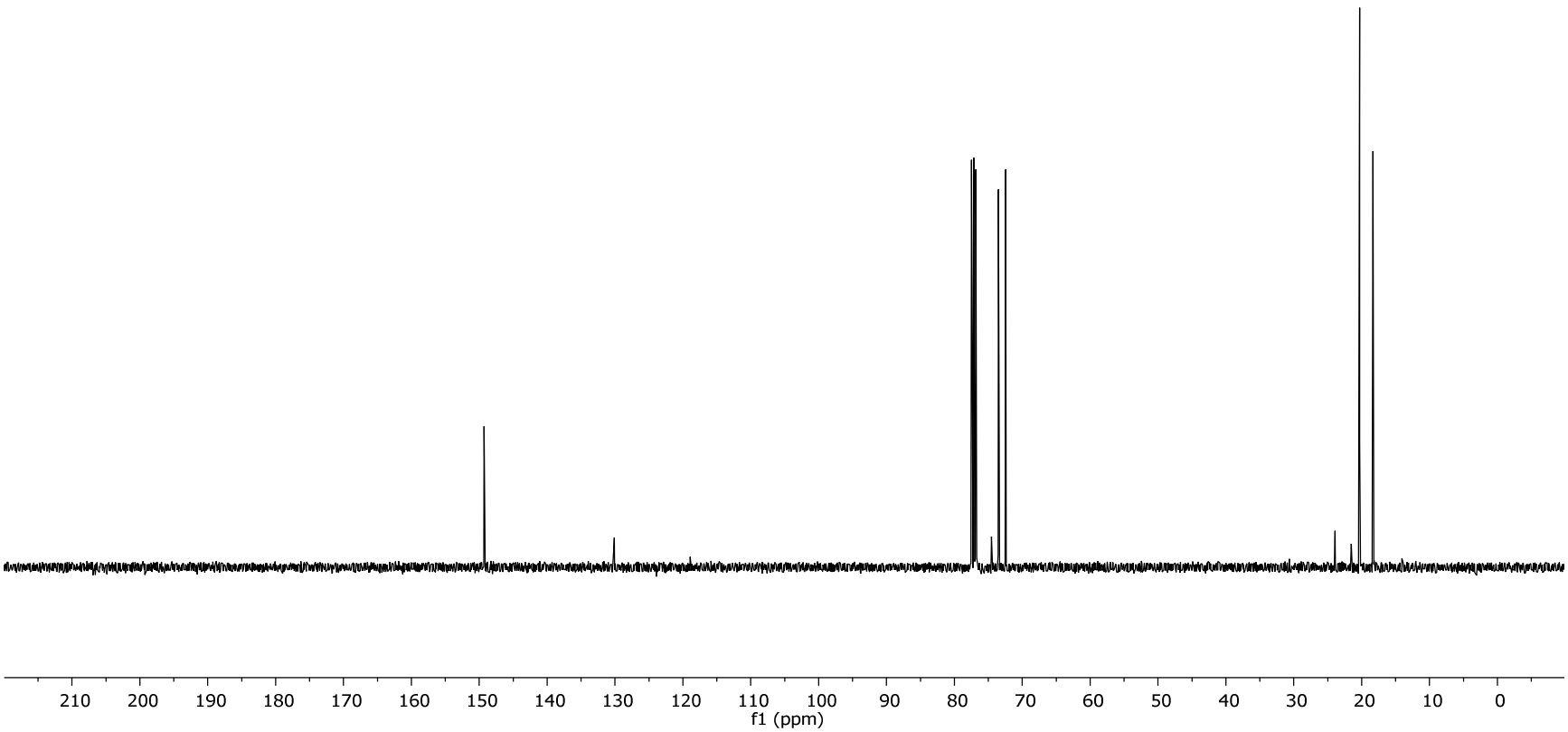
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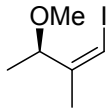
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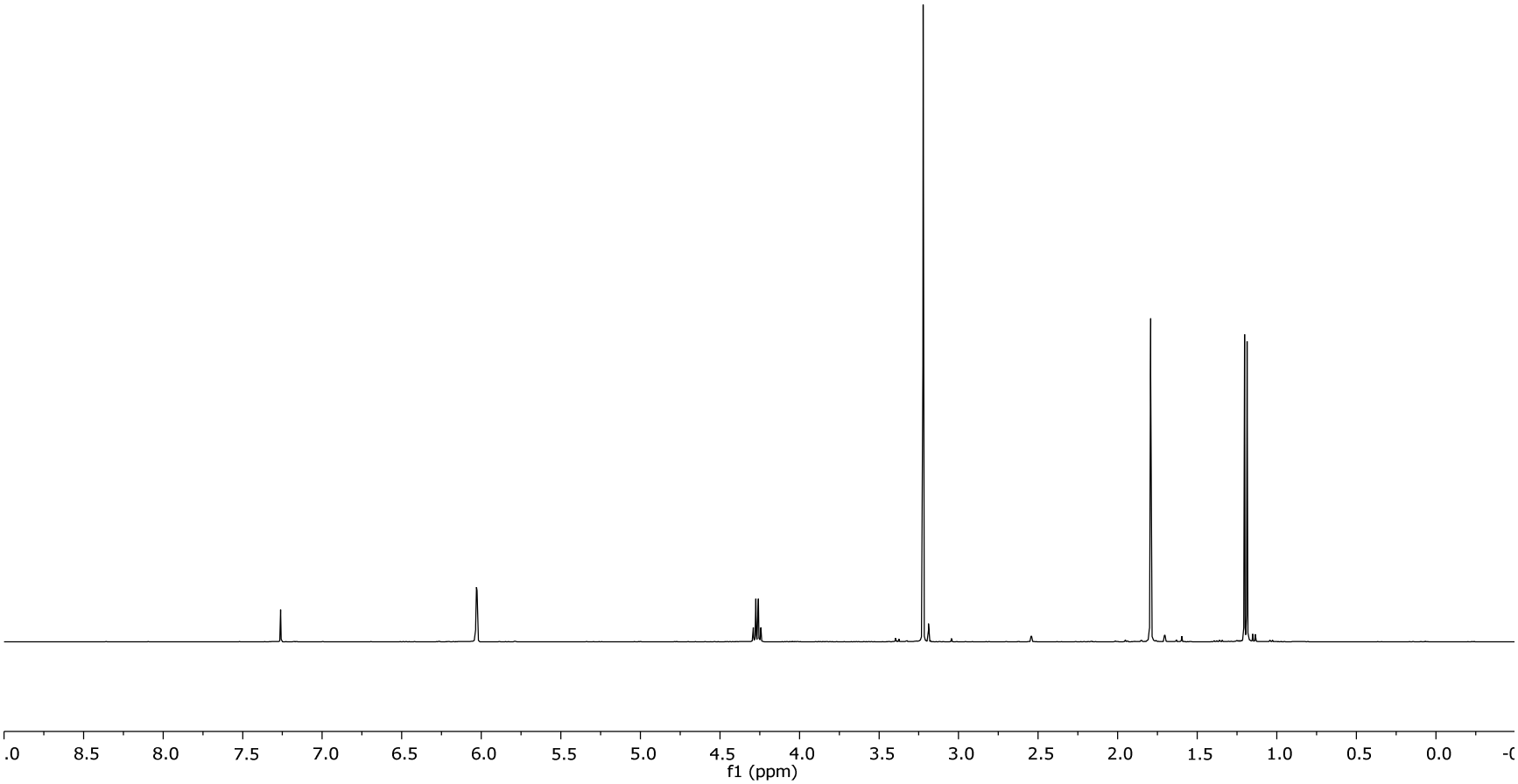
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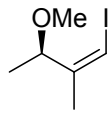
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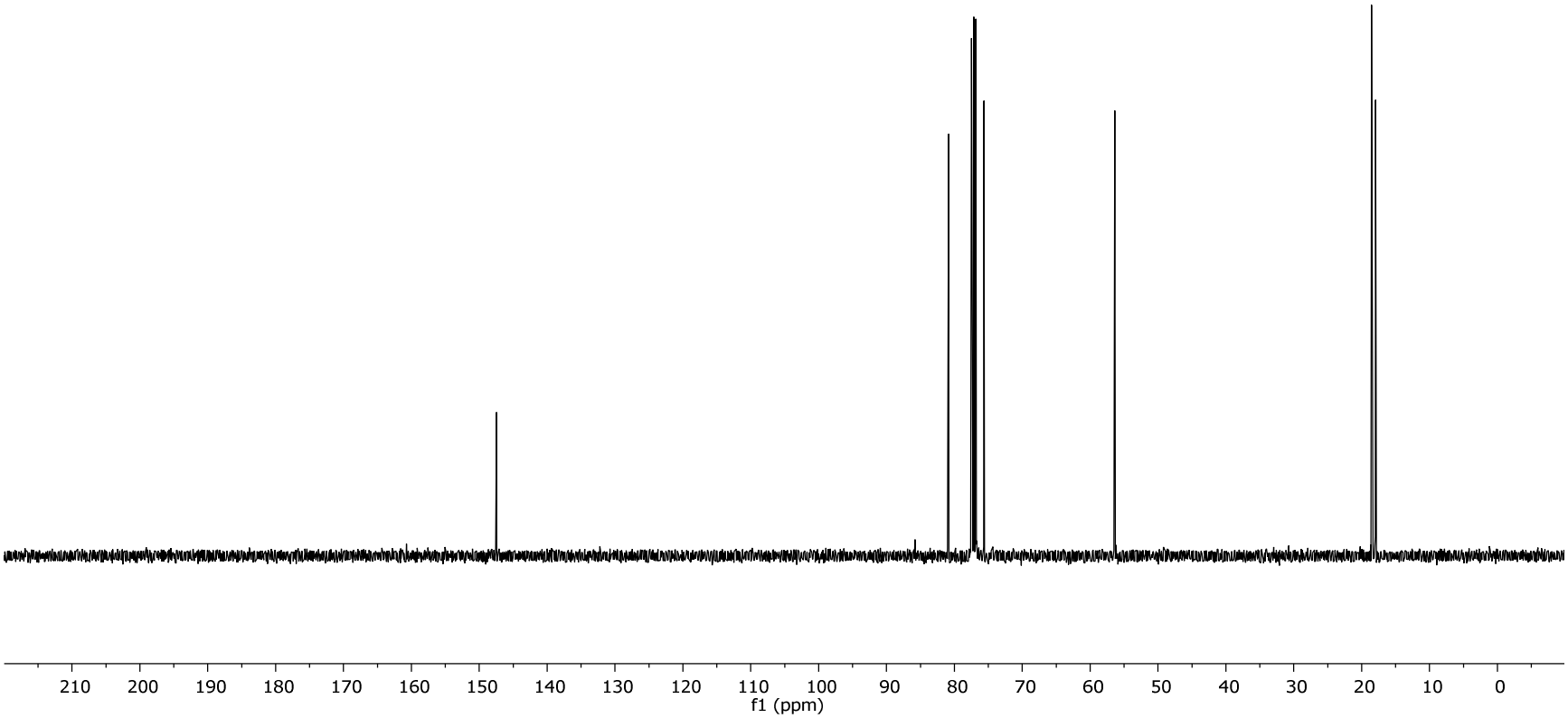
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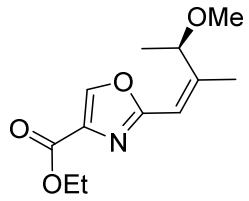
f1 (ppm)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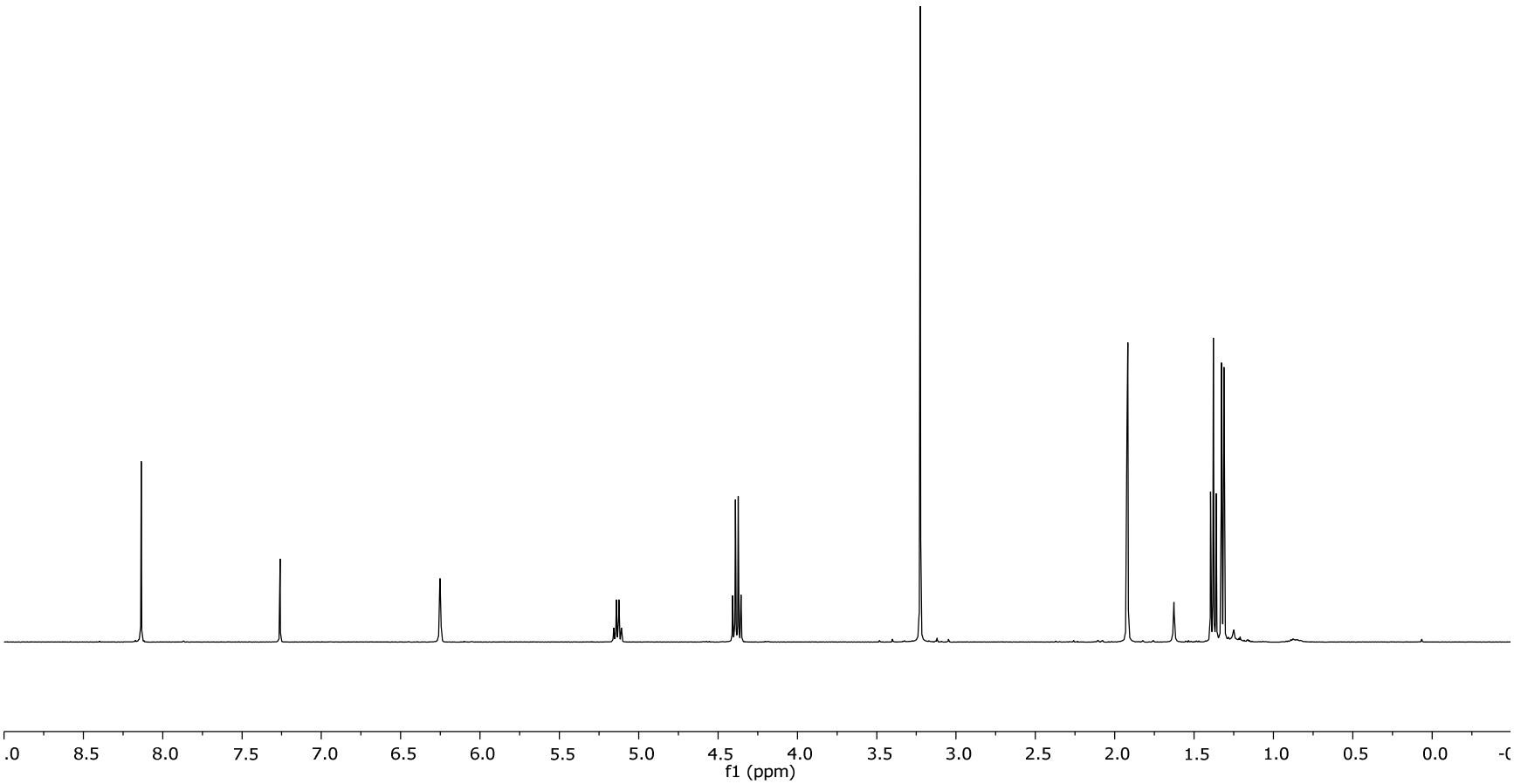
O
N
OEt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6.0
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1.0
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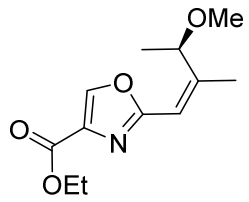
0.0
f1 (ppm)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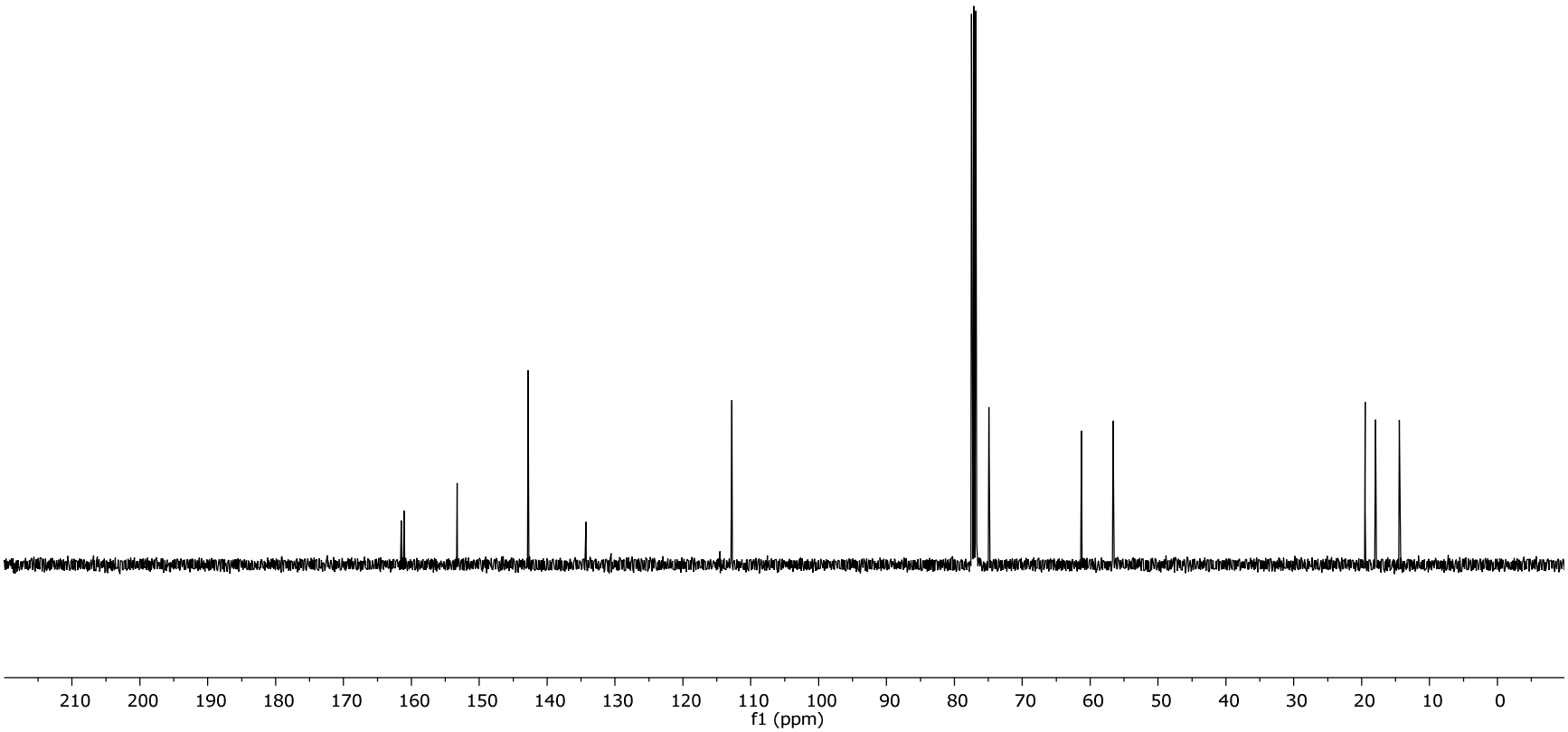
OEt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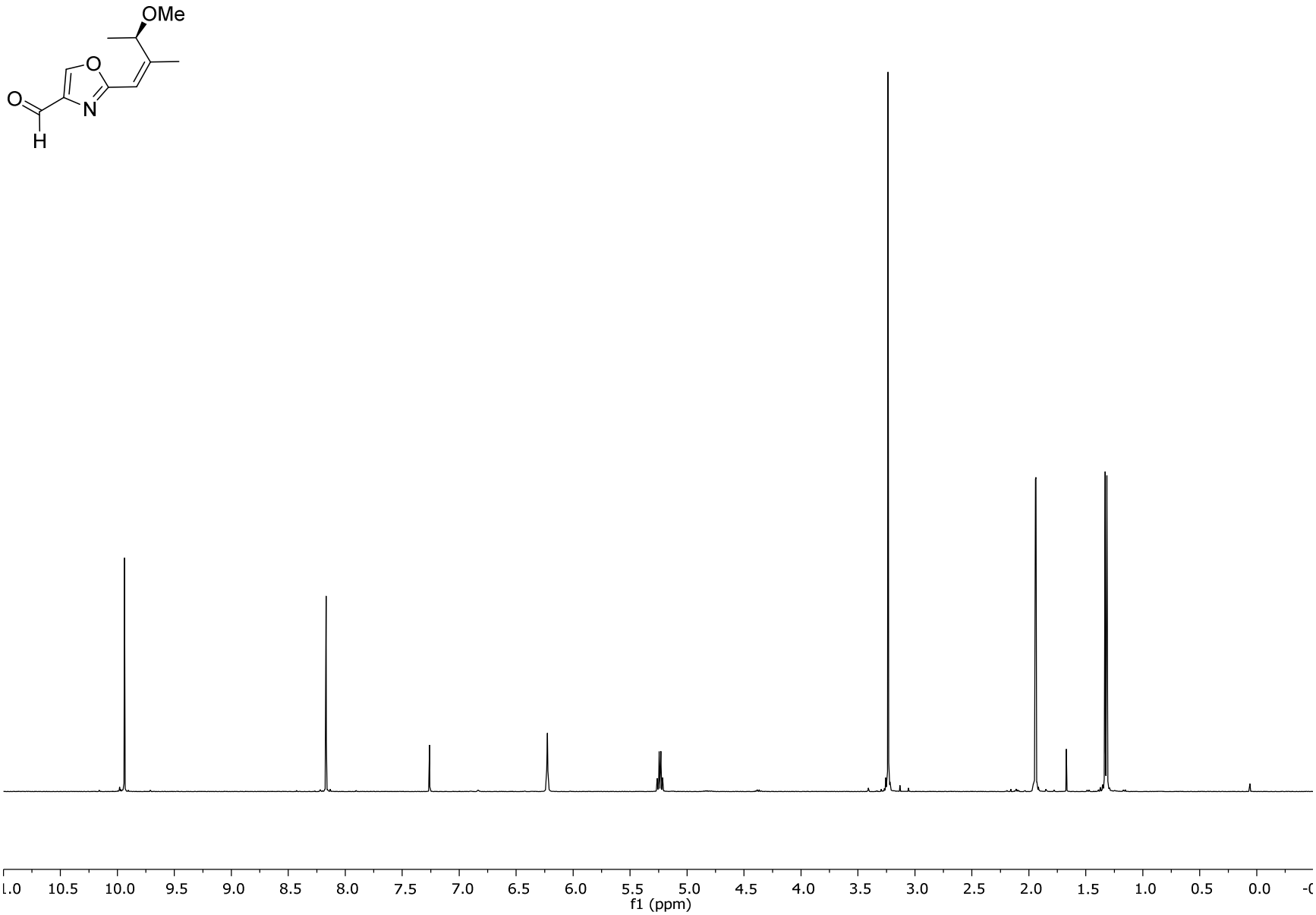
f1 (ppm)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O
H
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8.5
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6.5
6.0
5.5
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3.5
3.0
2.5
2.0
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1.0
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0.0
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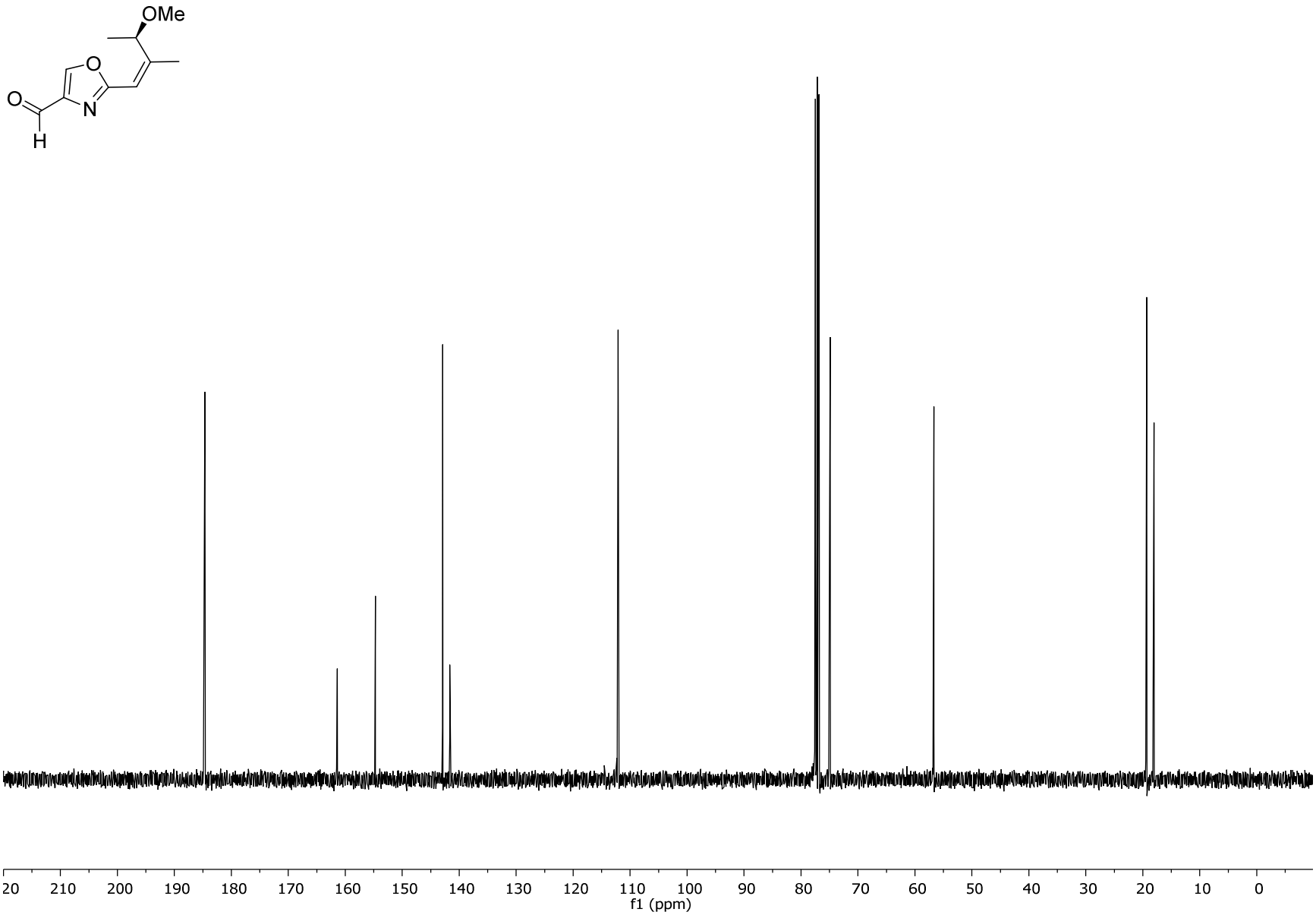
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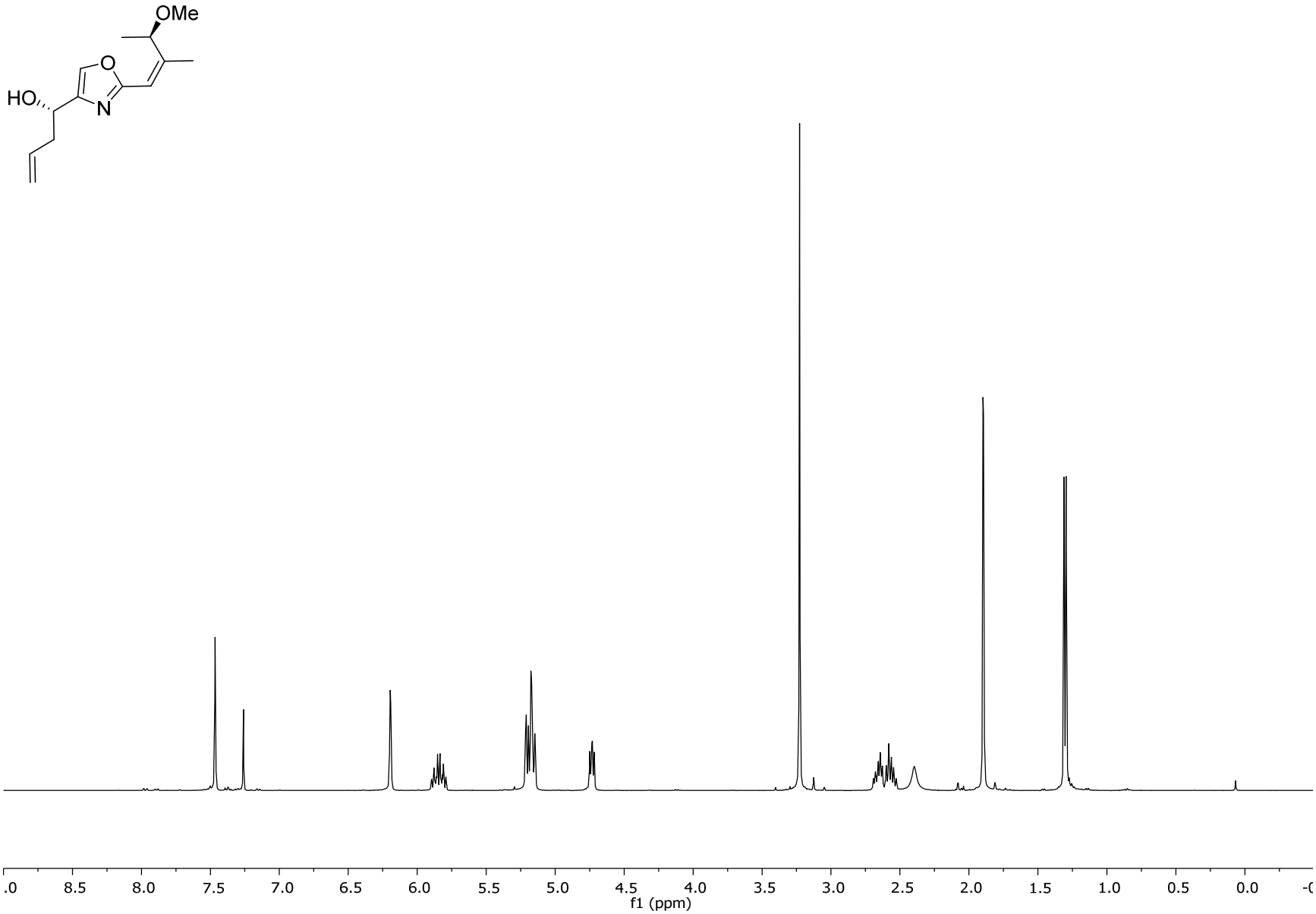
f1 (ppm)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O
N
HO
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6.5
6.0
5.5
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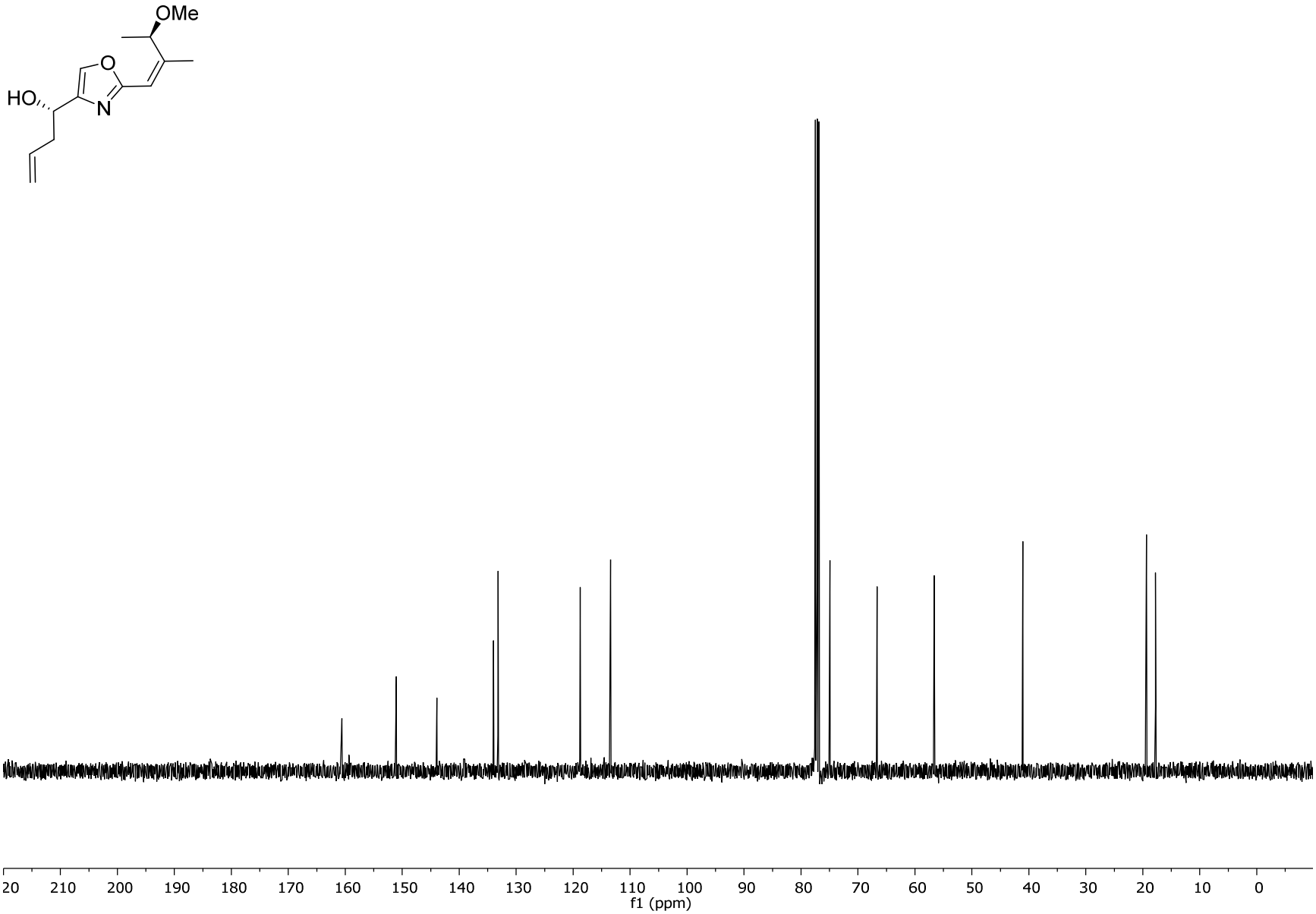
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OMe
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N
HO
220
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180
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50
40
30
20
10
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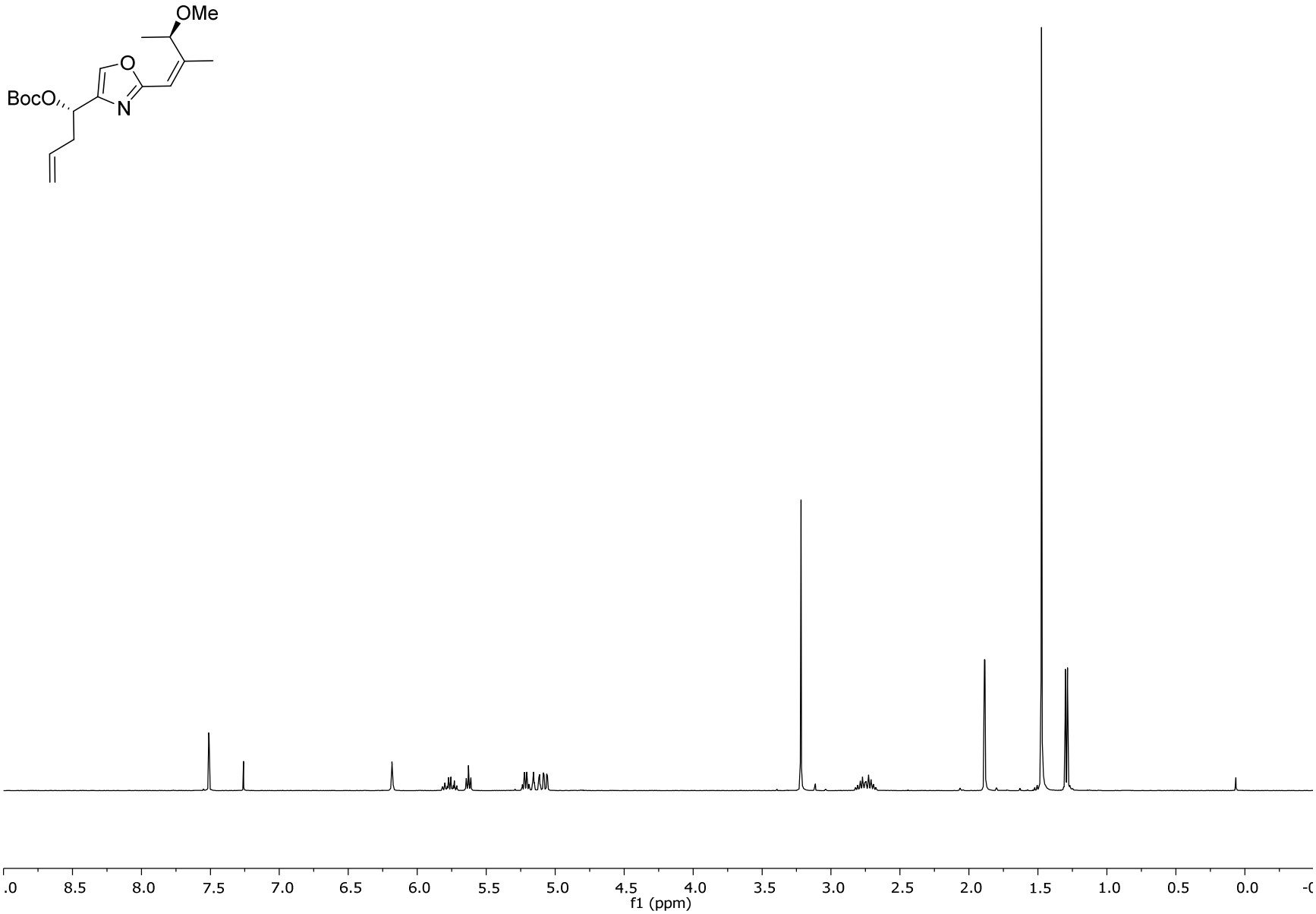
f1 (ppm)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BocO
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5.5
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2.5
2.0
1.5
1.0
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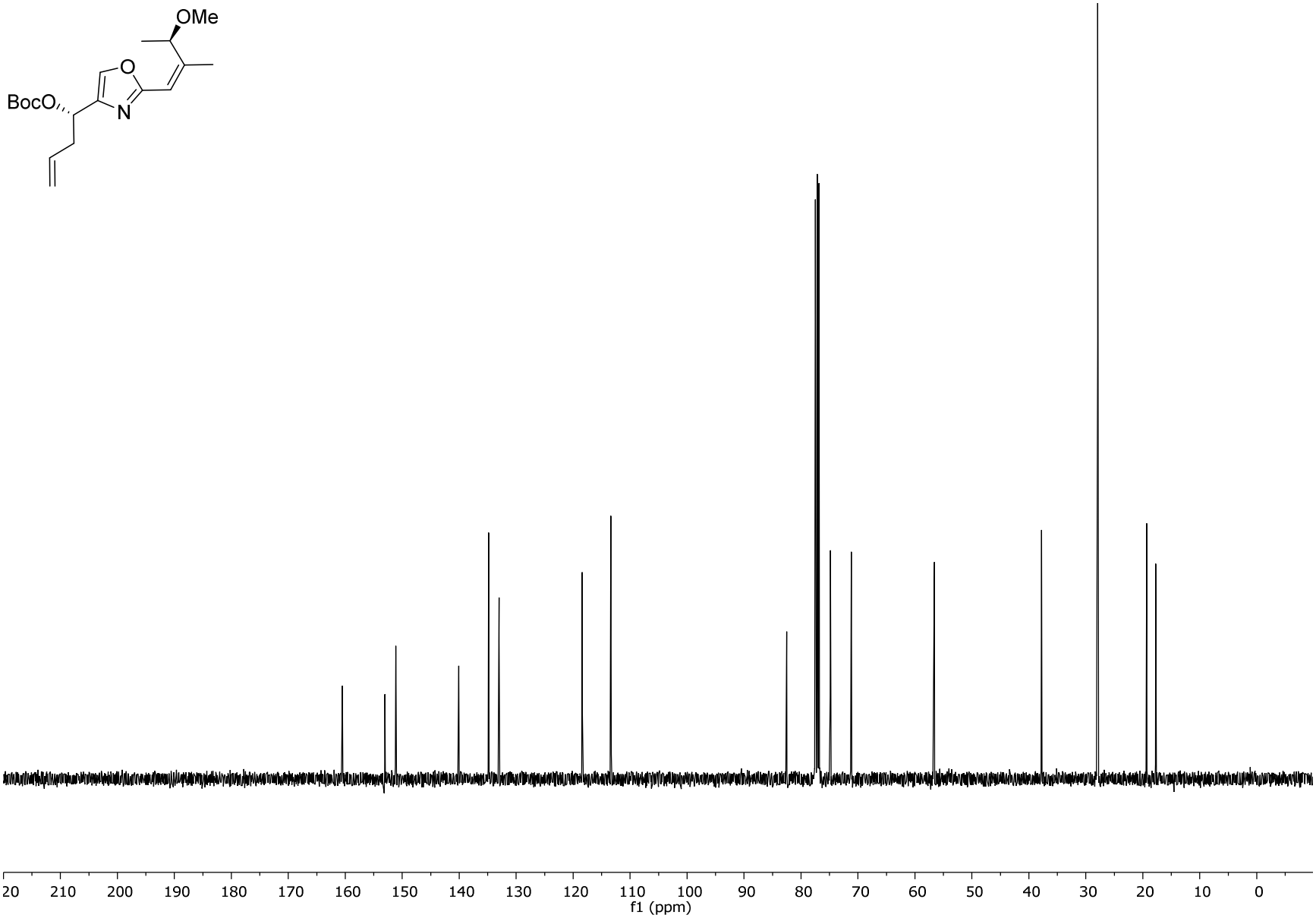
0.0
f1 (ppm)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O
N
BocO
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210
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190
180
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130
120
110
100
90
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50
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10
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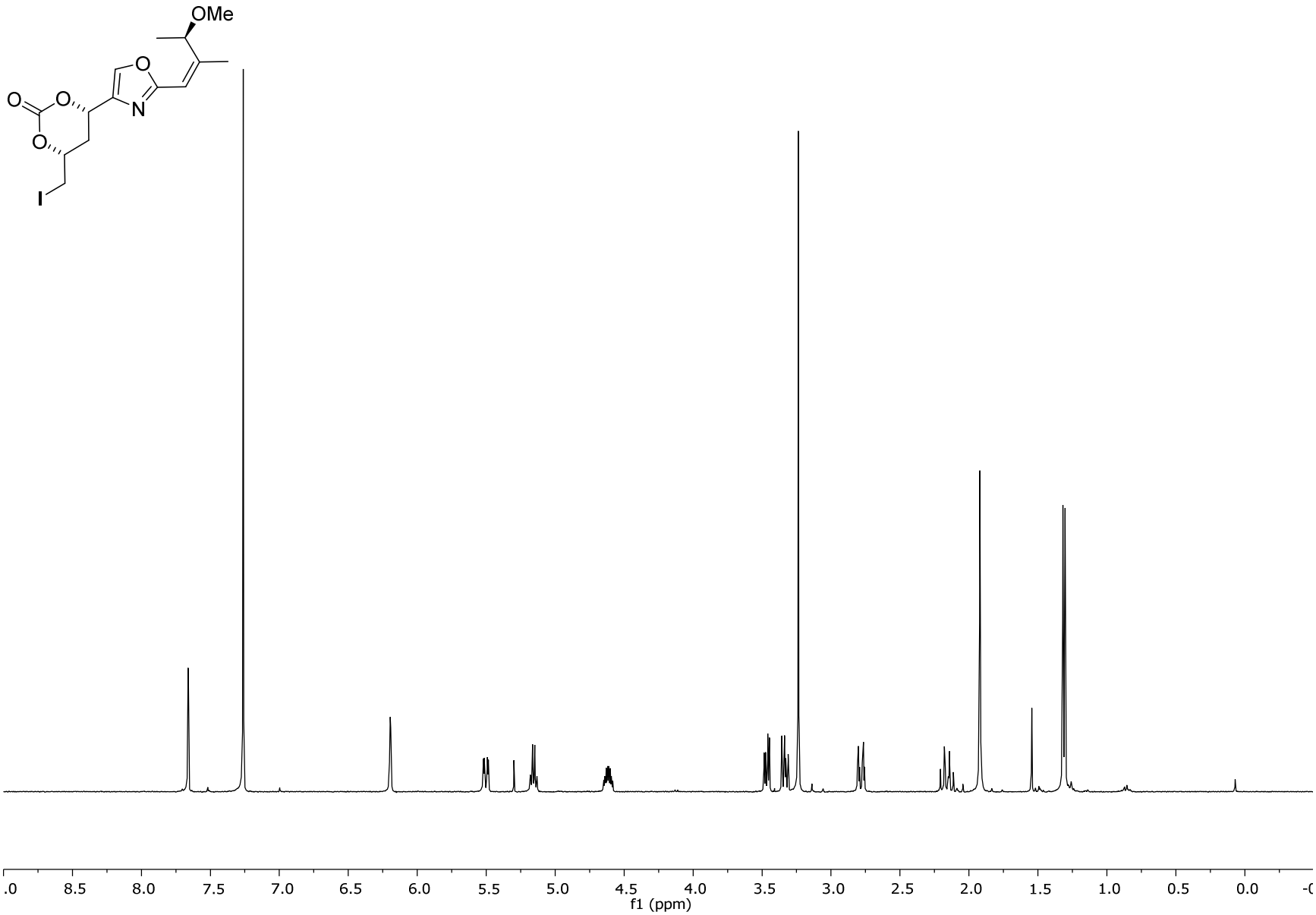
f1 (ppm)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O
O
O
N
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7.0
6.5
6.0
5.5
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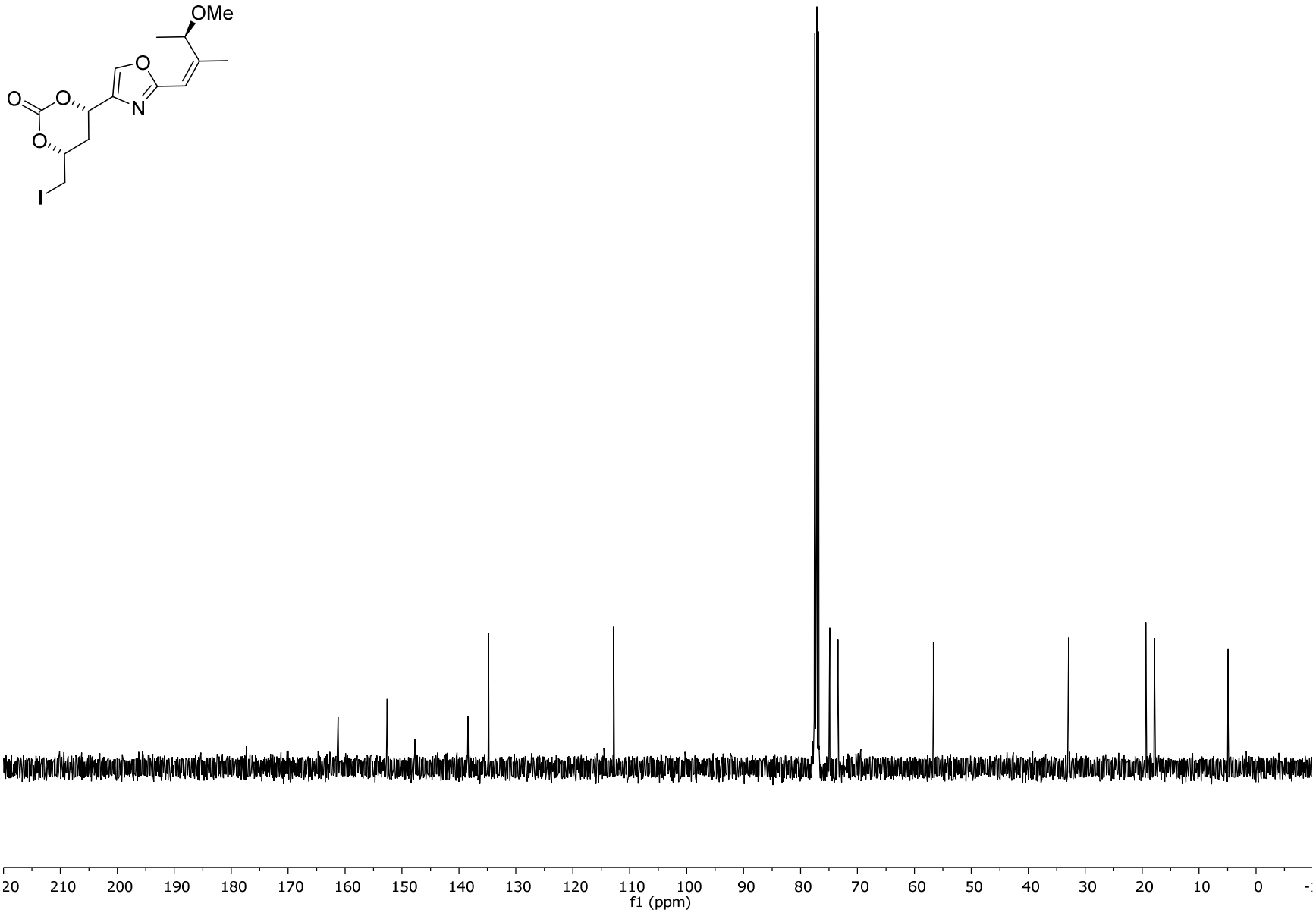
0.0
f1 (ppm)


OMe
O
O
O
O
N
I
220
210
200
190
180
170
160
150
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130
120
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10
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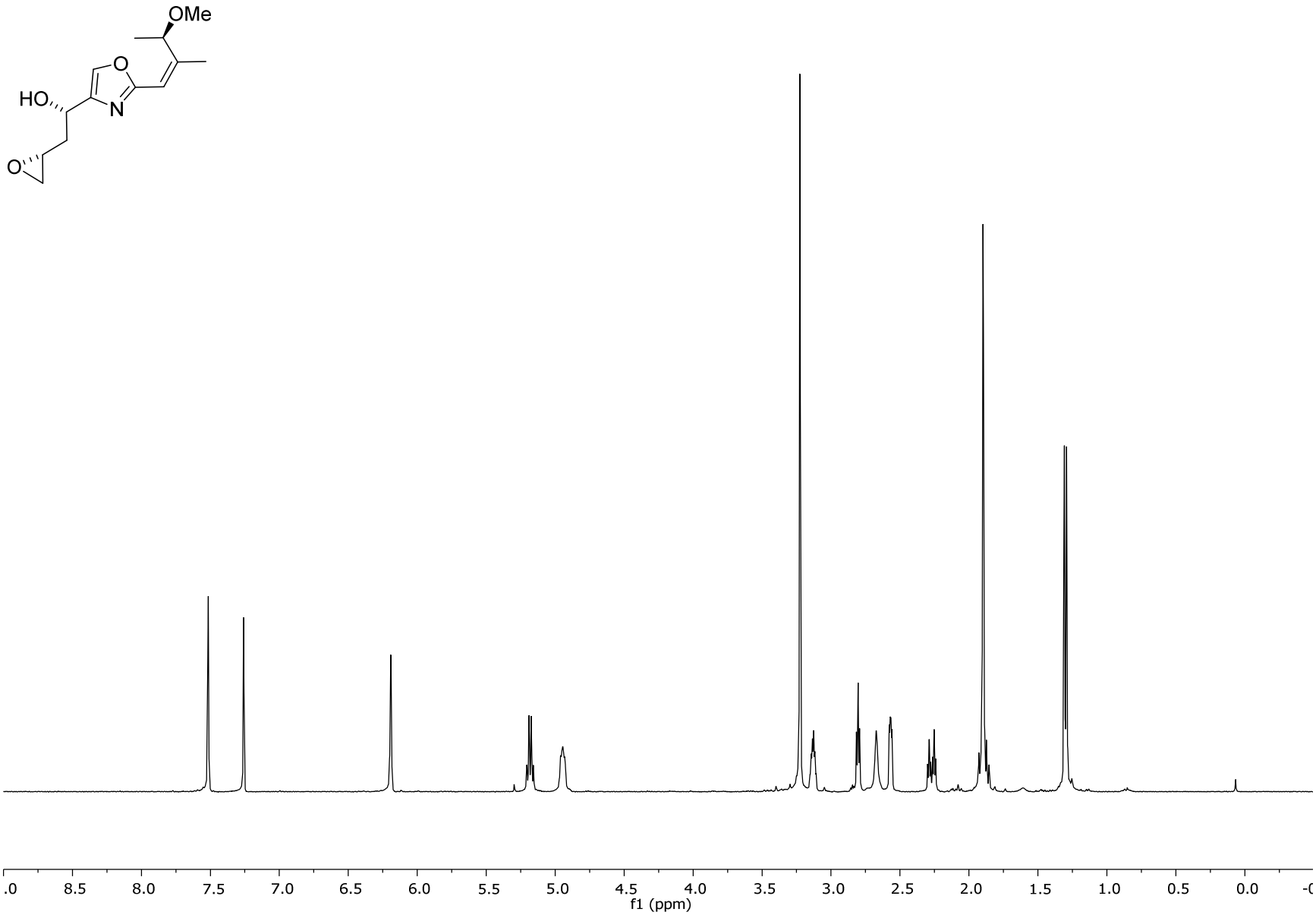
f1 (ppm)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HO
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N
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.5
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2.5
2.0
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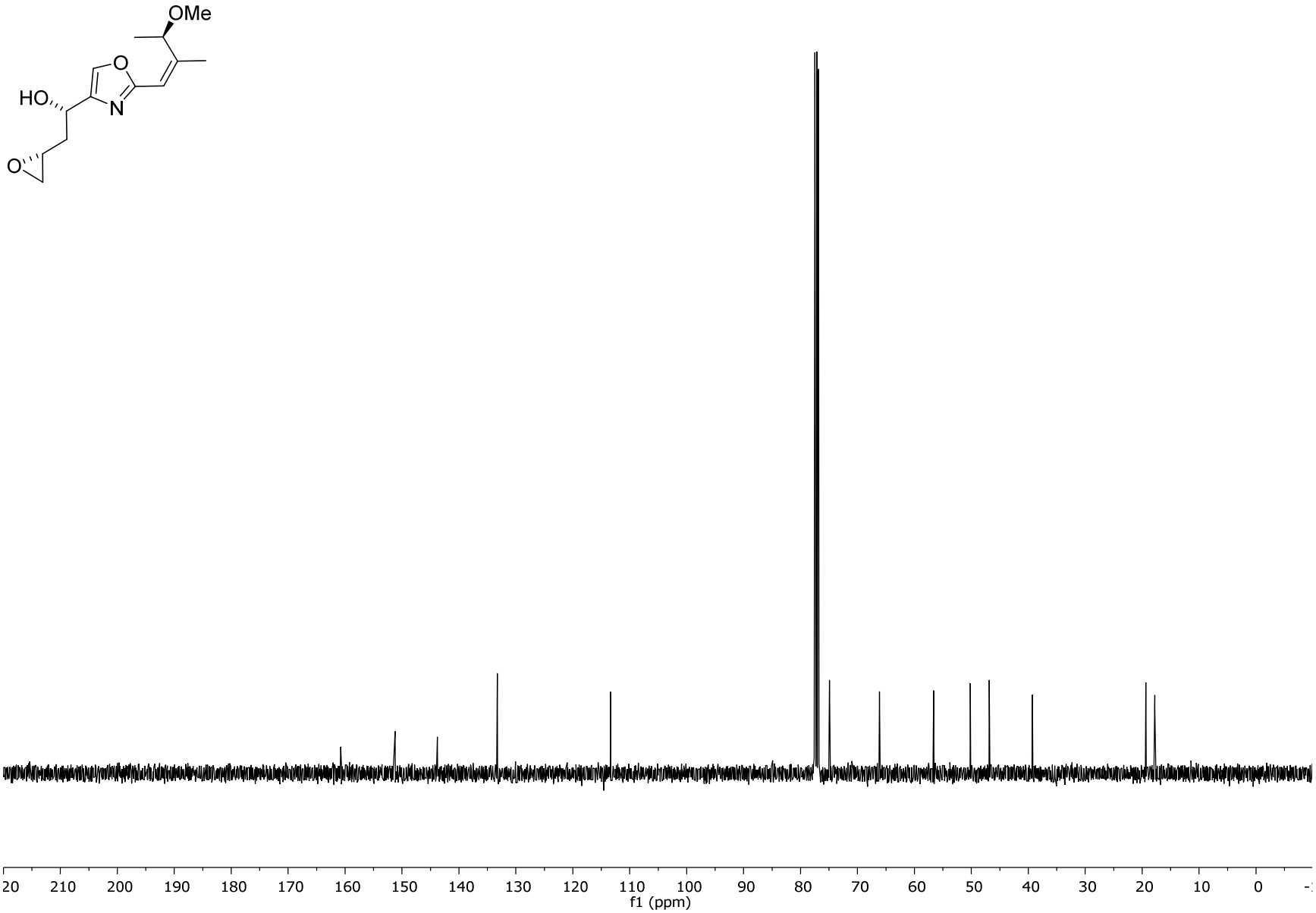
0.0
f1 (ppm)


OMe
HO
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N
O
220
210
200
190
180
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130
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70
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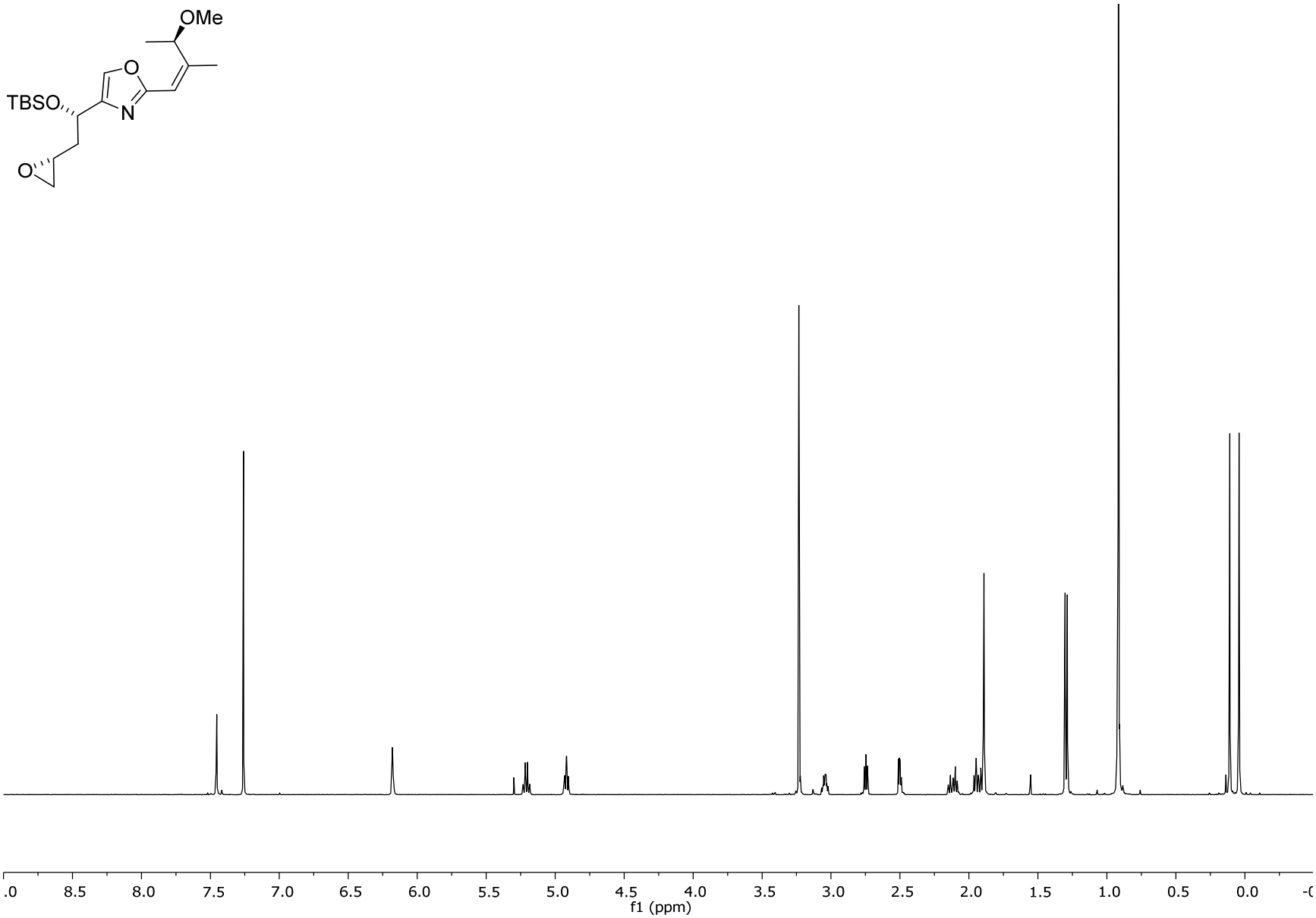
f1 (ppm)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TBSO
O
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O
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7.5
7.0
6.5
6.0
5.5
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3.0
2.5
2.0
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1.0
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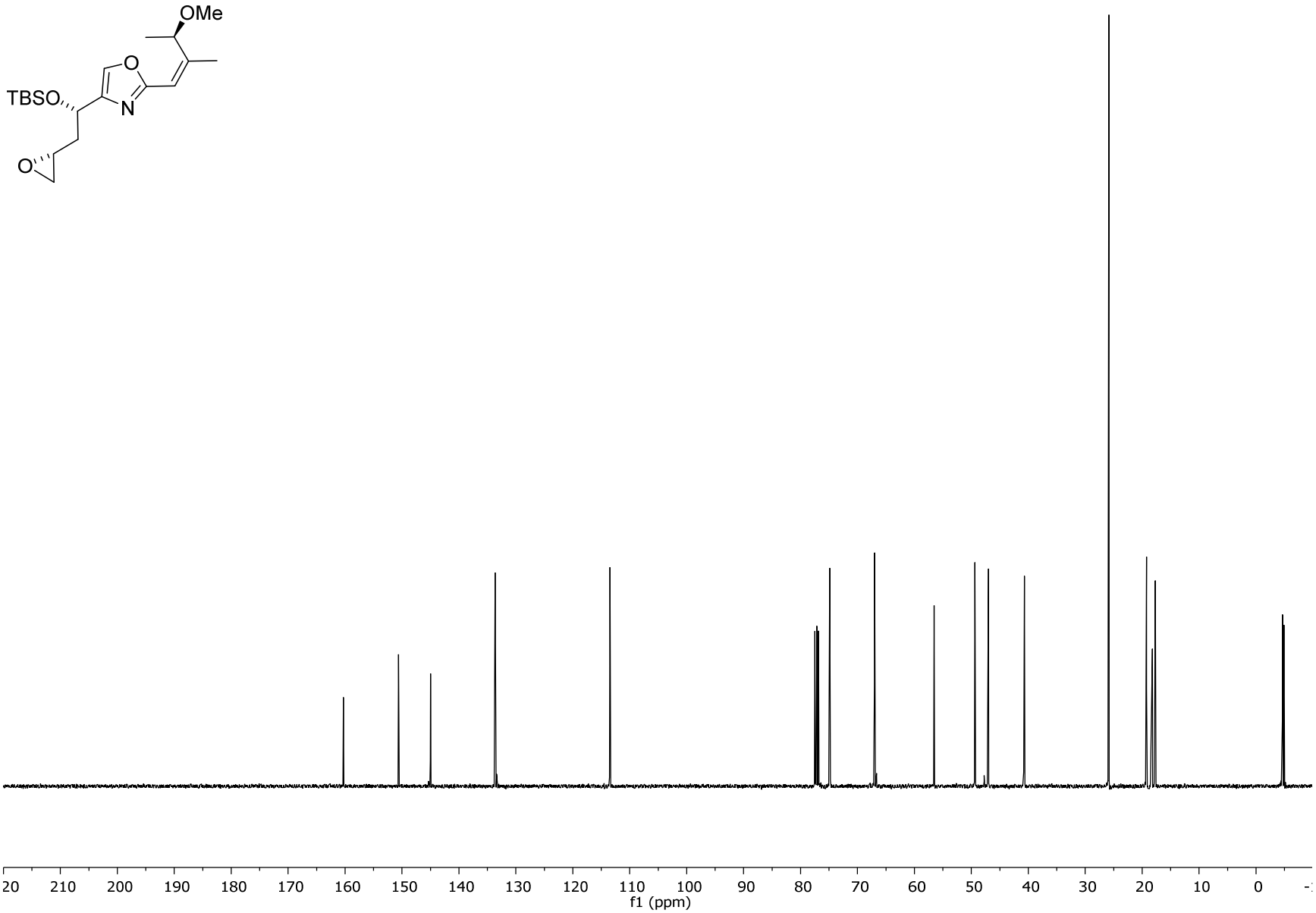
0.0
f1 (ppm)


OMe
TBSO
O
N
O
220
210
200
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180
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90
80
70
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50
40
30
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10
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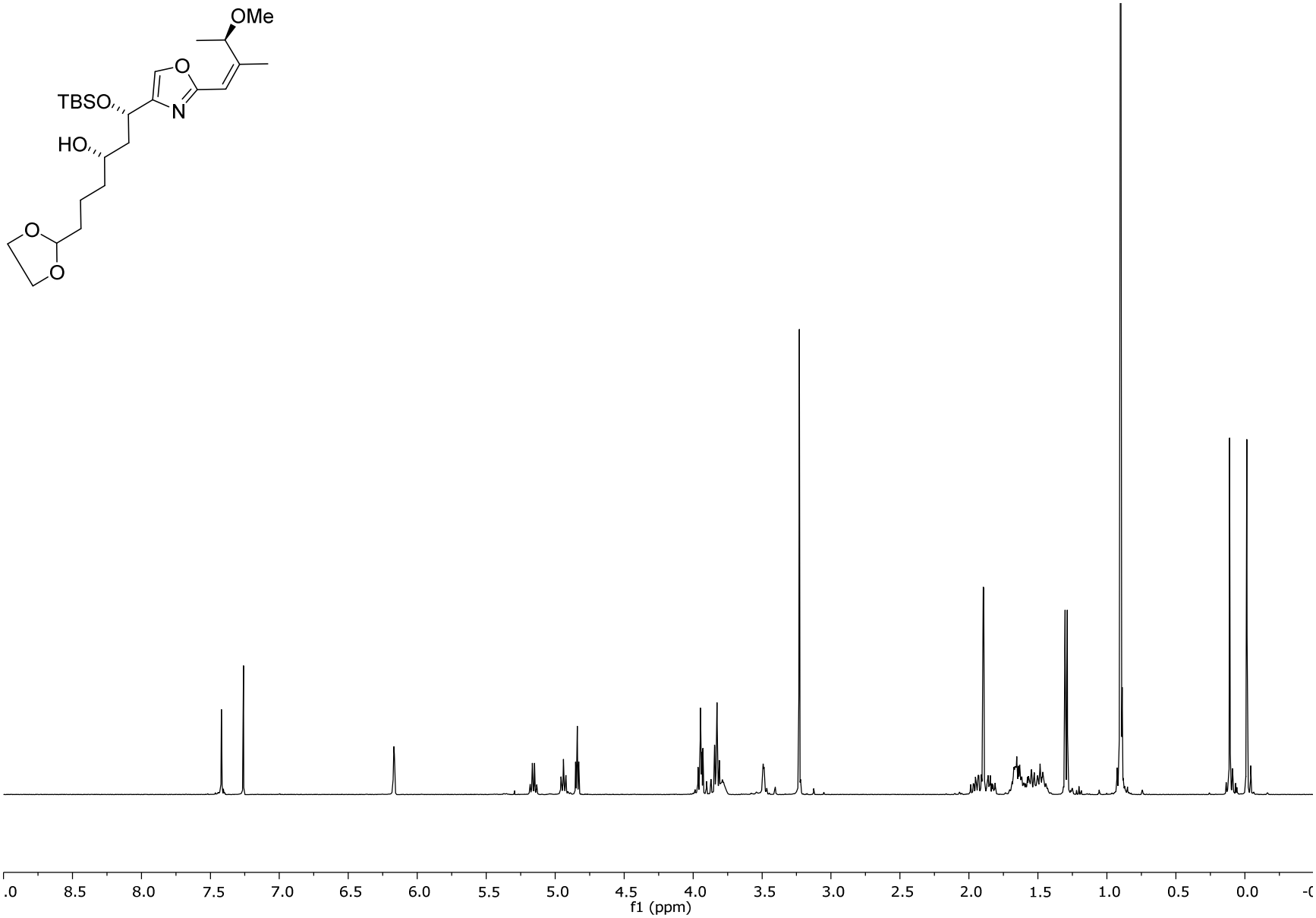
f1 (ppm)


OMe
O
TBSO
N
HO
O
O
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8.0
7.5
7.0
6.5
6.0
5.5
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2.0
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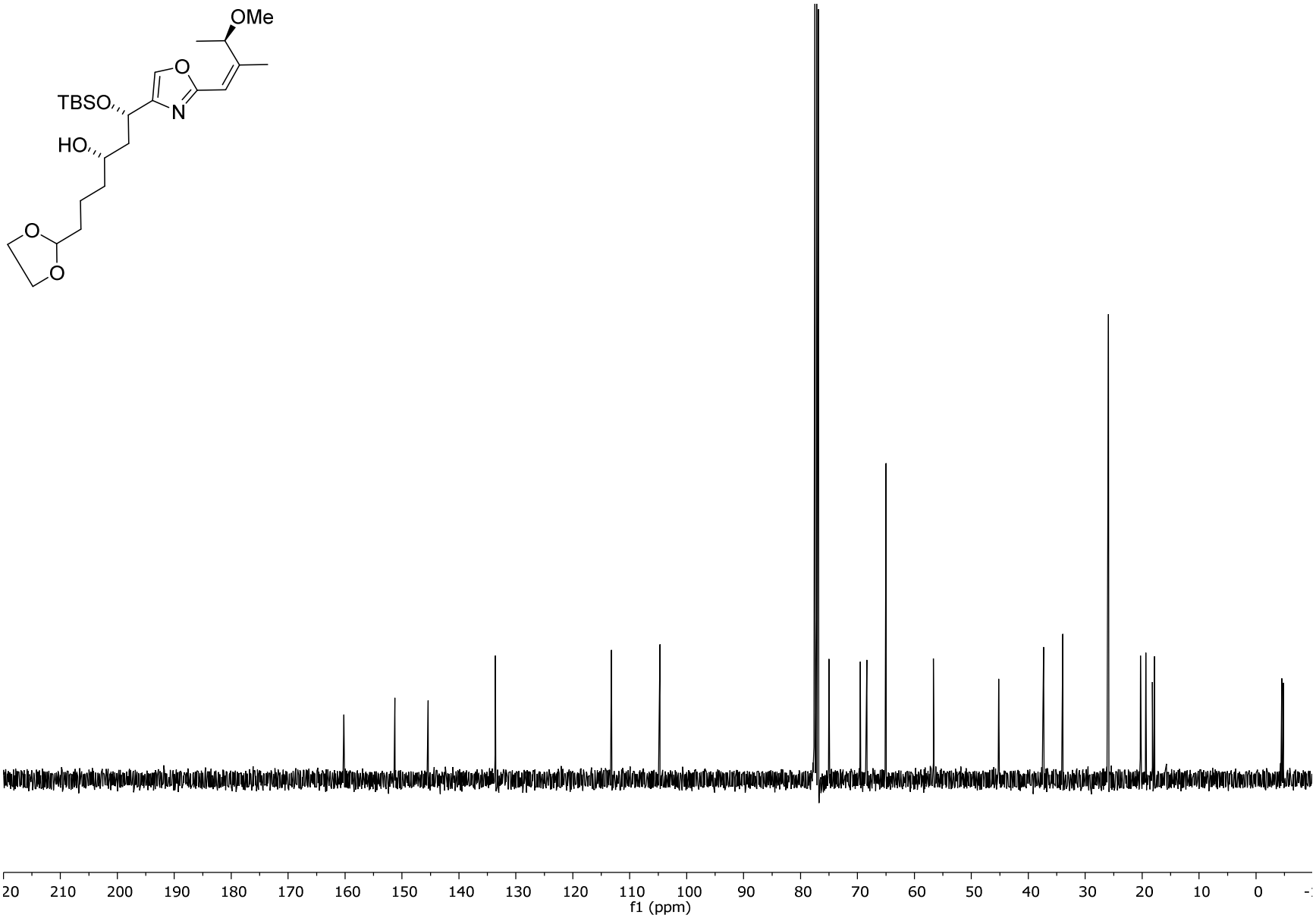
f1 (ppm)


OMe
O
TBSO
N
HO
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O
220
210
200
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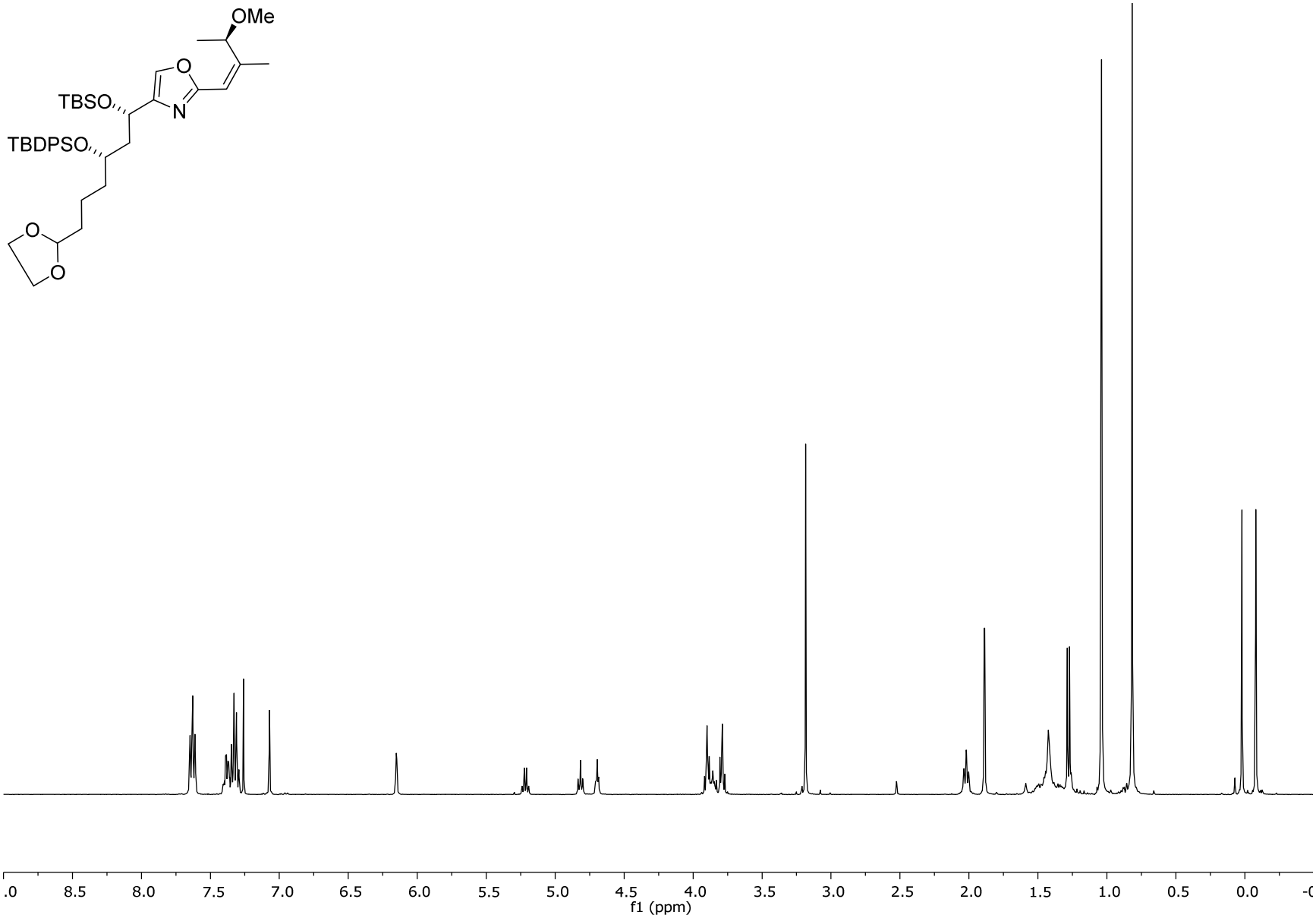
f1 (ppm)


OMe
O
N
TBSO
TBDPSO
O
O
.0
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8.0
7.5
7.0
6.5
6.0
5.5
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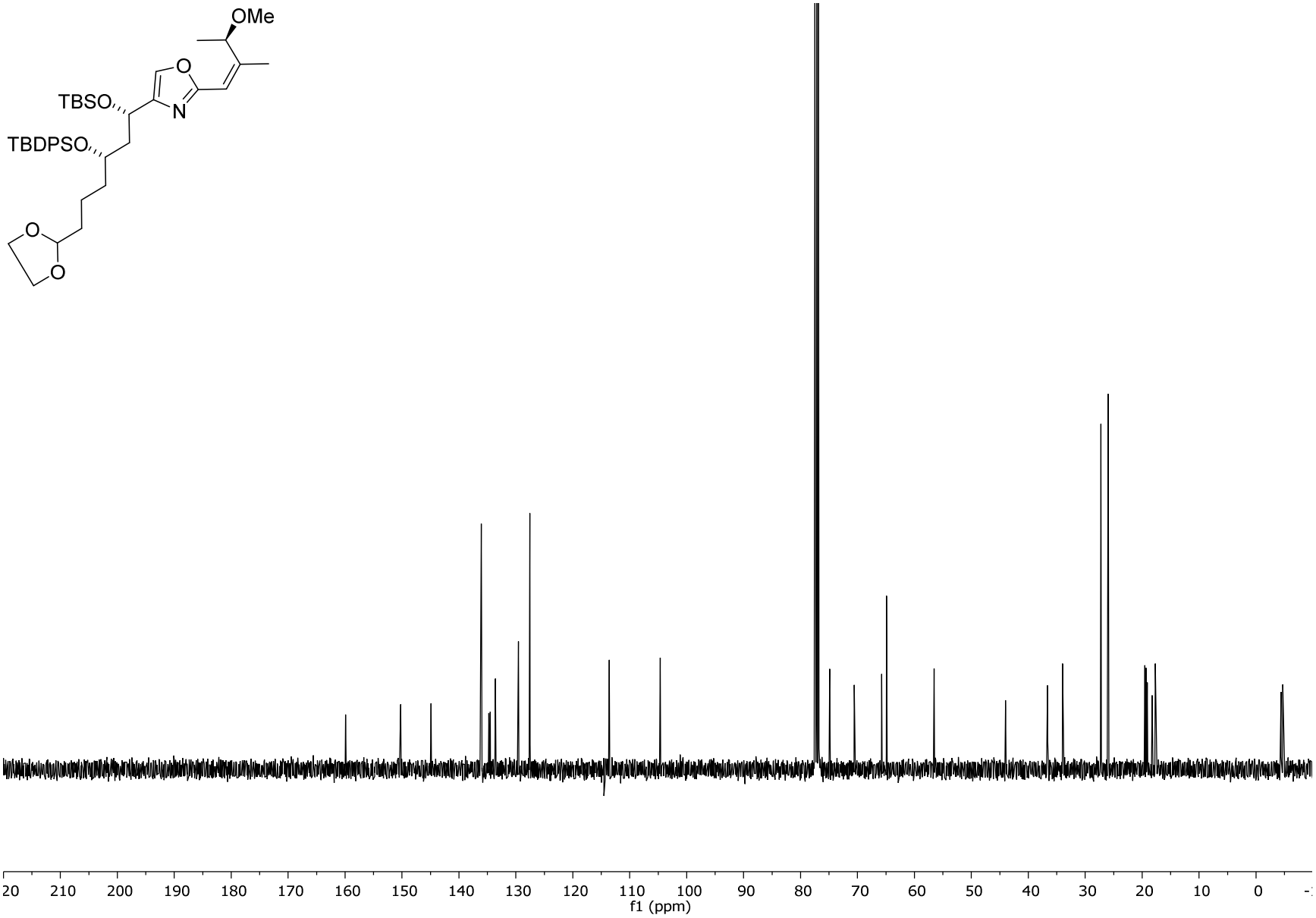
0.0
f1 (ppm)


OMe
O
N
TBSO
TBDPSO
O
O
220
210
200
190
180
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110
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90
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50
40
30
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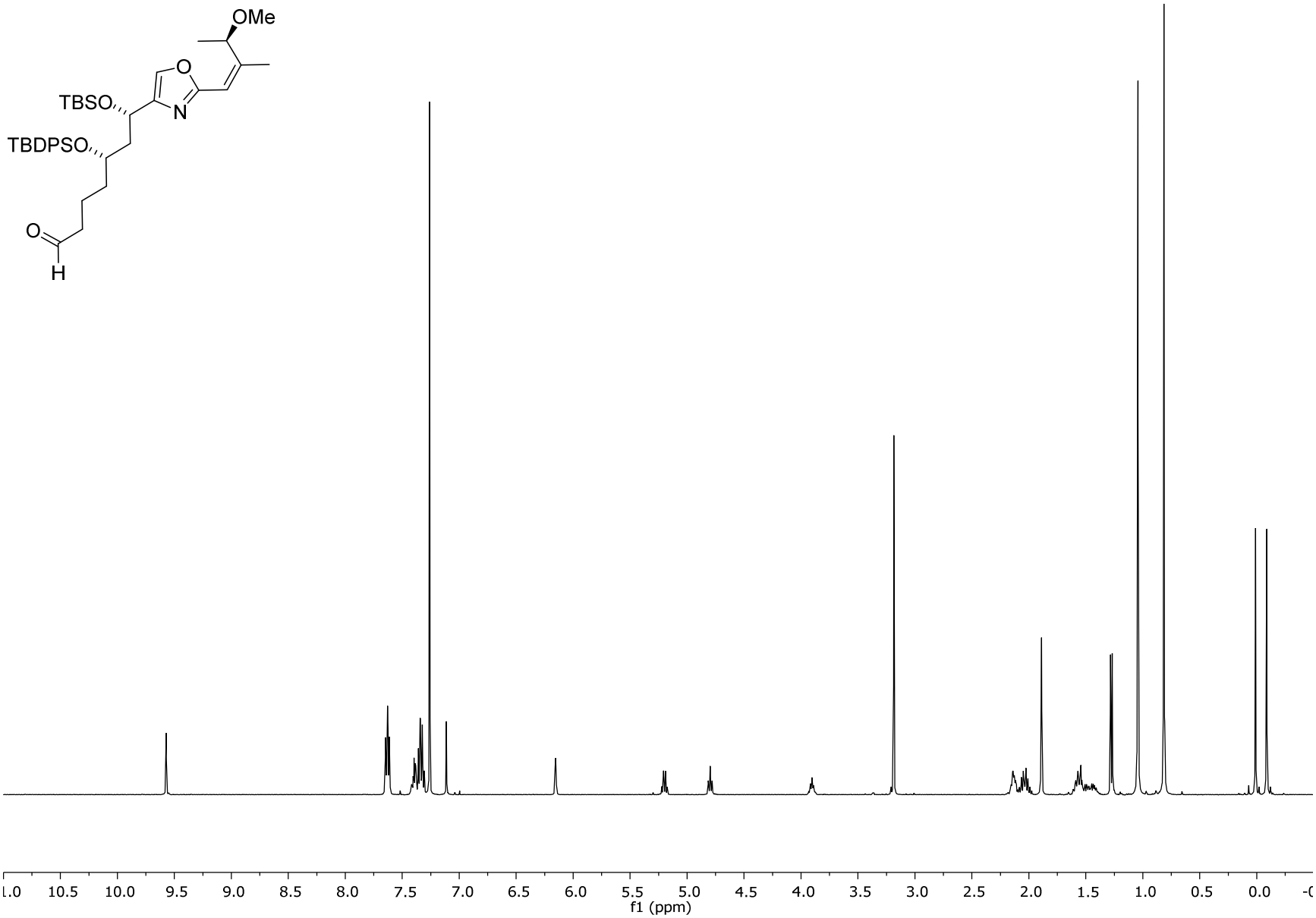
10
0
f1 (ppm)


OMe
O
N
TBSO
TBDPSO
O
H
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9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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2.0
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1.0
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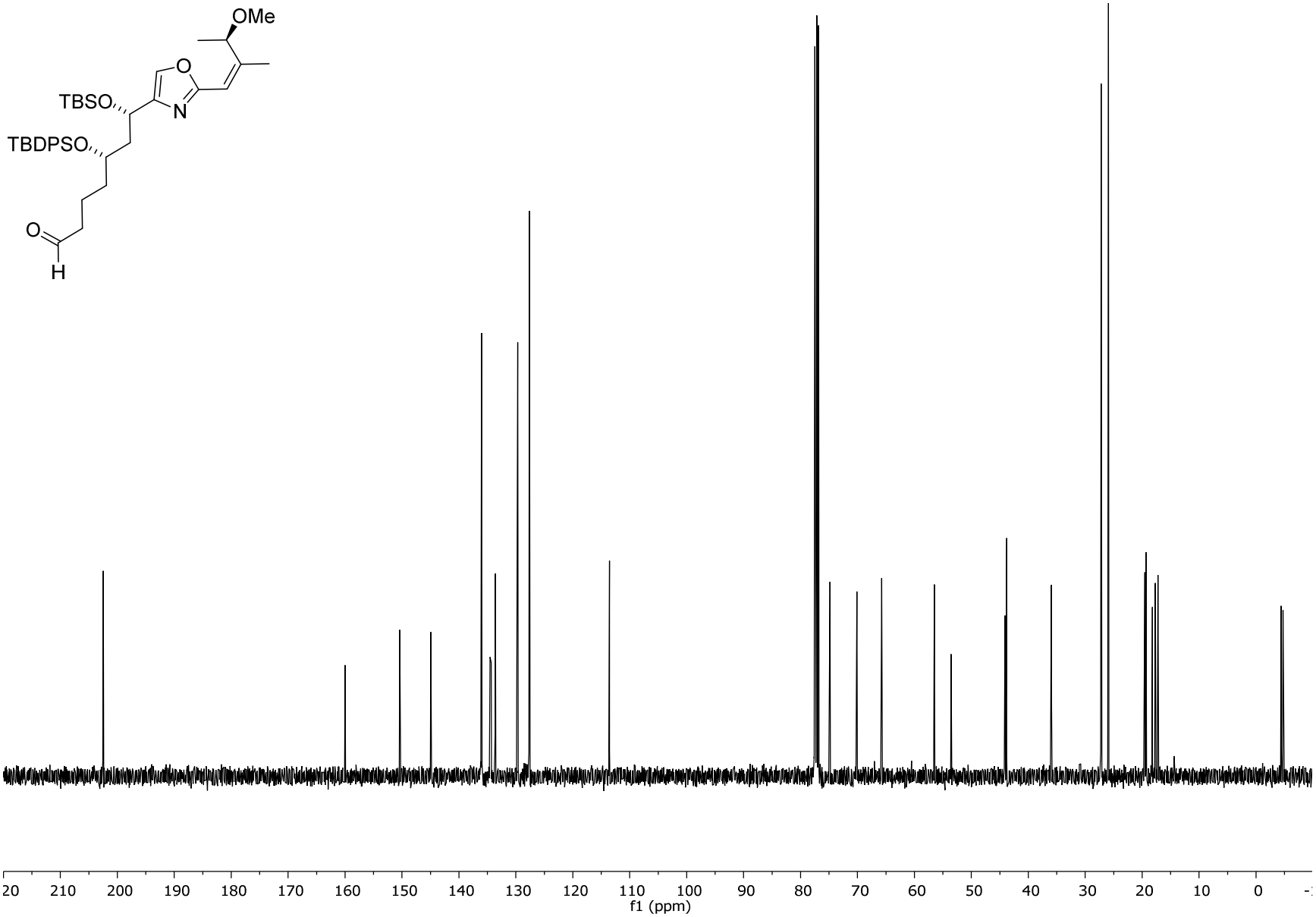
OMe
O
N
TBSO
TBDPSO
O
H
220
210
200
190
180
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110
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50
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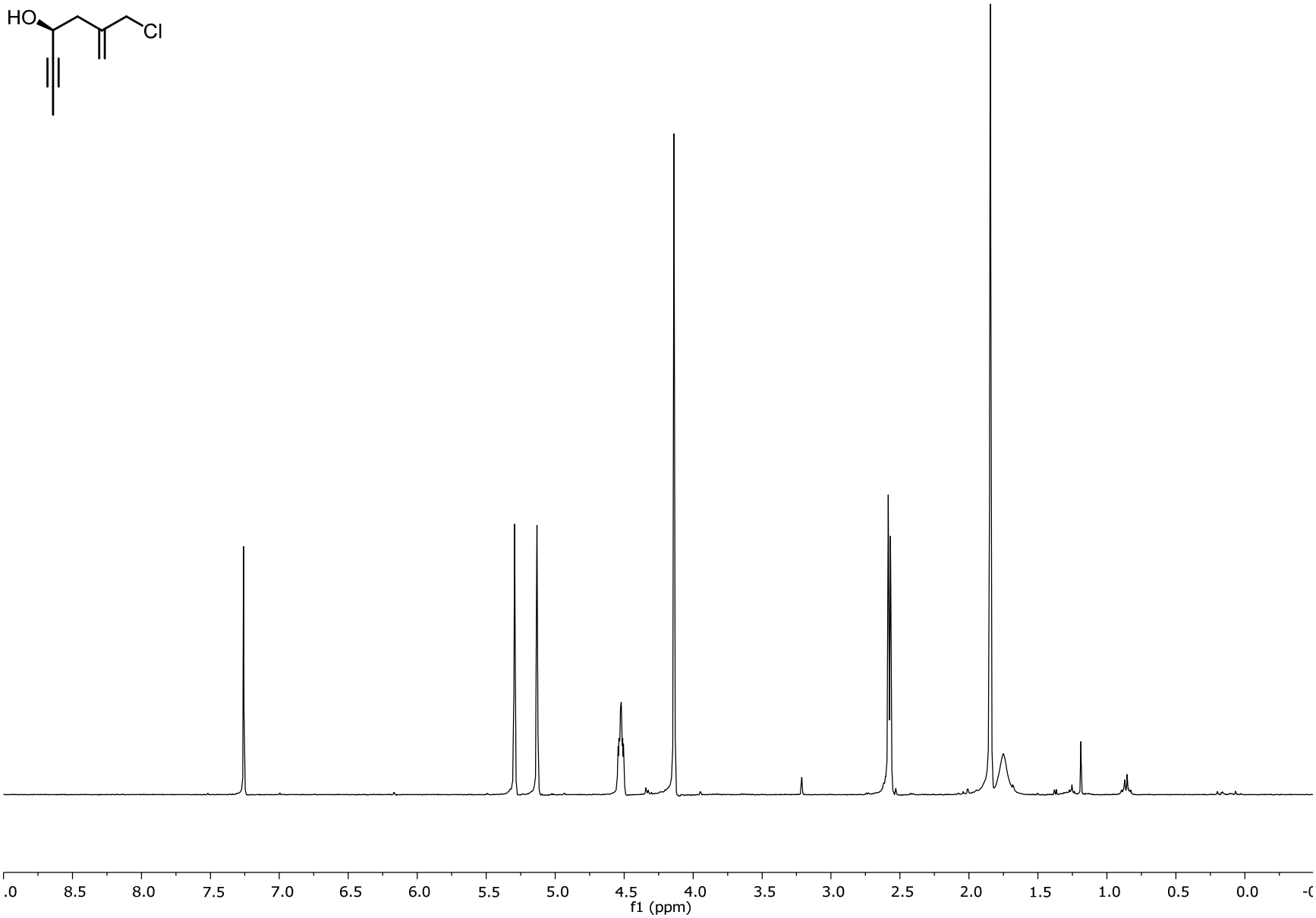
f1 (ppm)


HO
Cl
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5.5
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2.5
2.0
1.5
1.0
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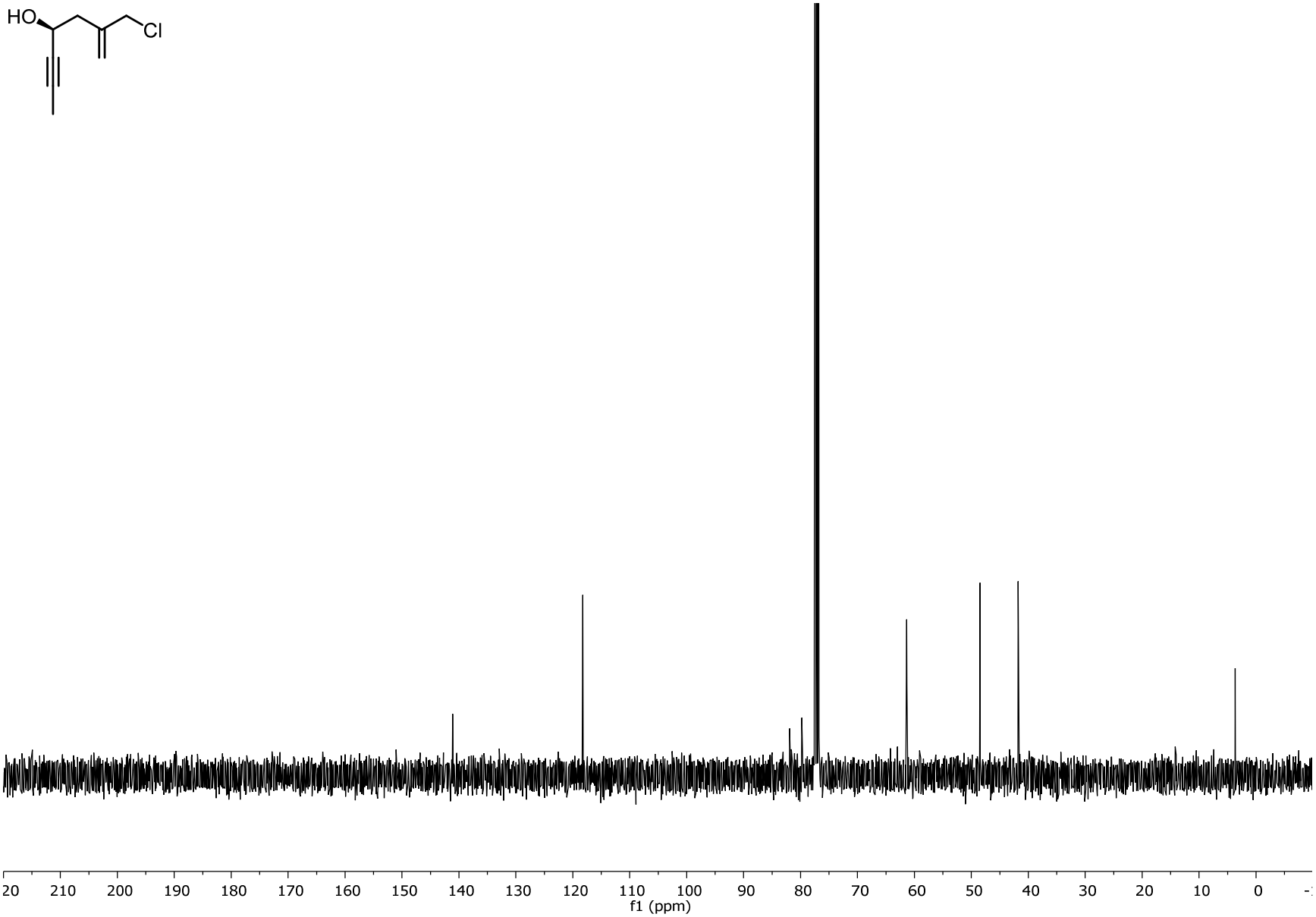
0.0
f1 (ppm)


HO
Cl
220
210
200
190
180
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150
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130
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110
100
90
80
70
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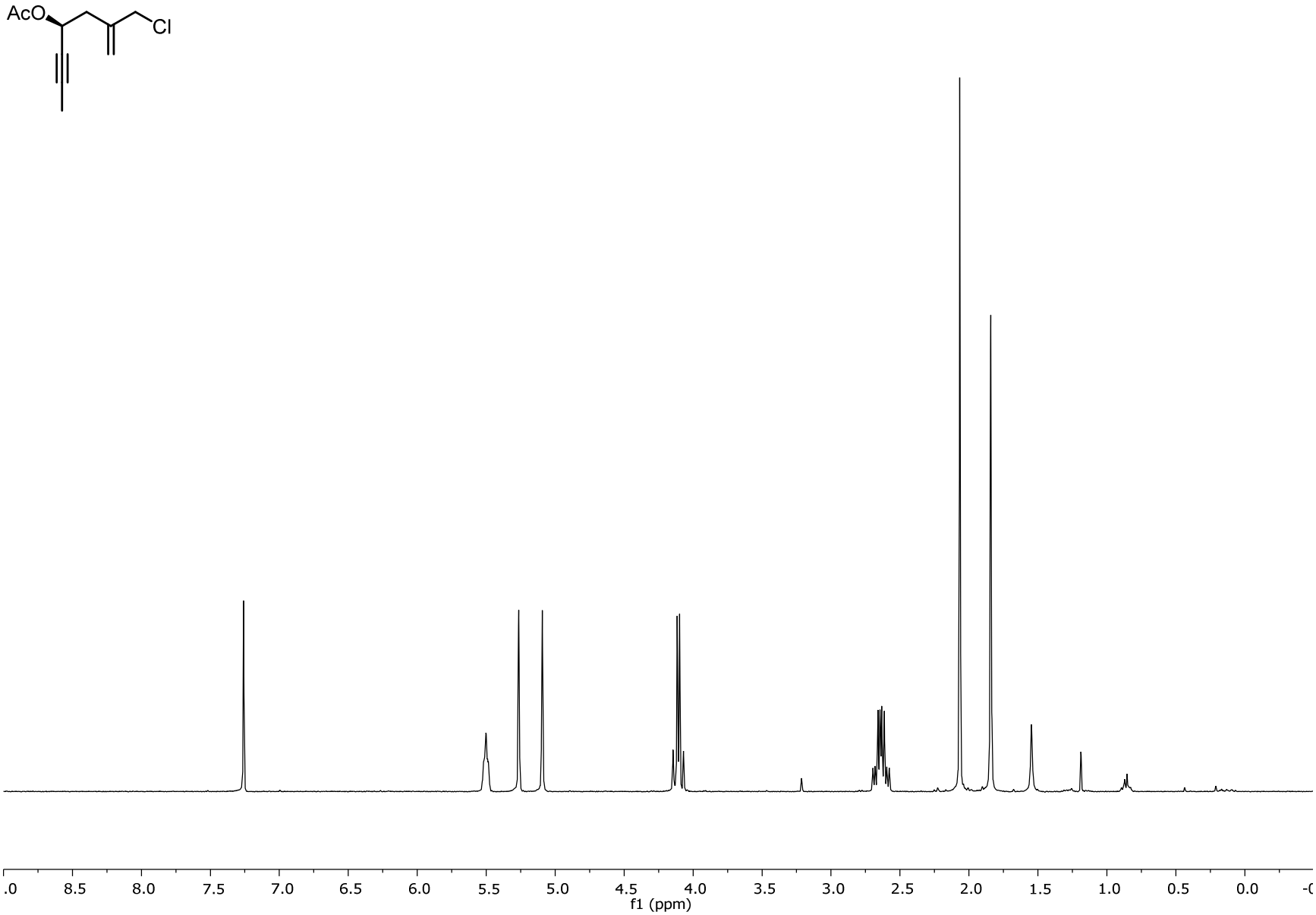
50
40
30
20
10
0
f1 (ppm)


AcO
Cl
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7.5
7.0
6.5
6.0
5.5
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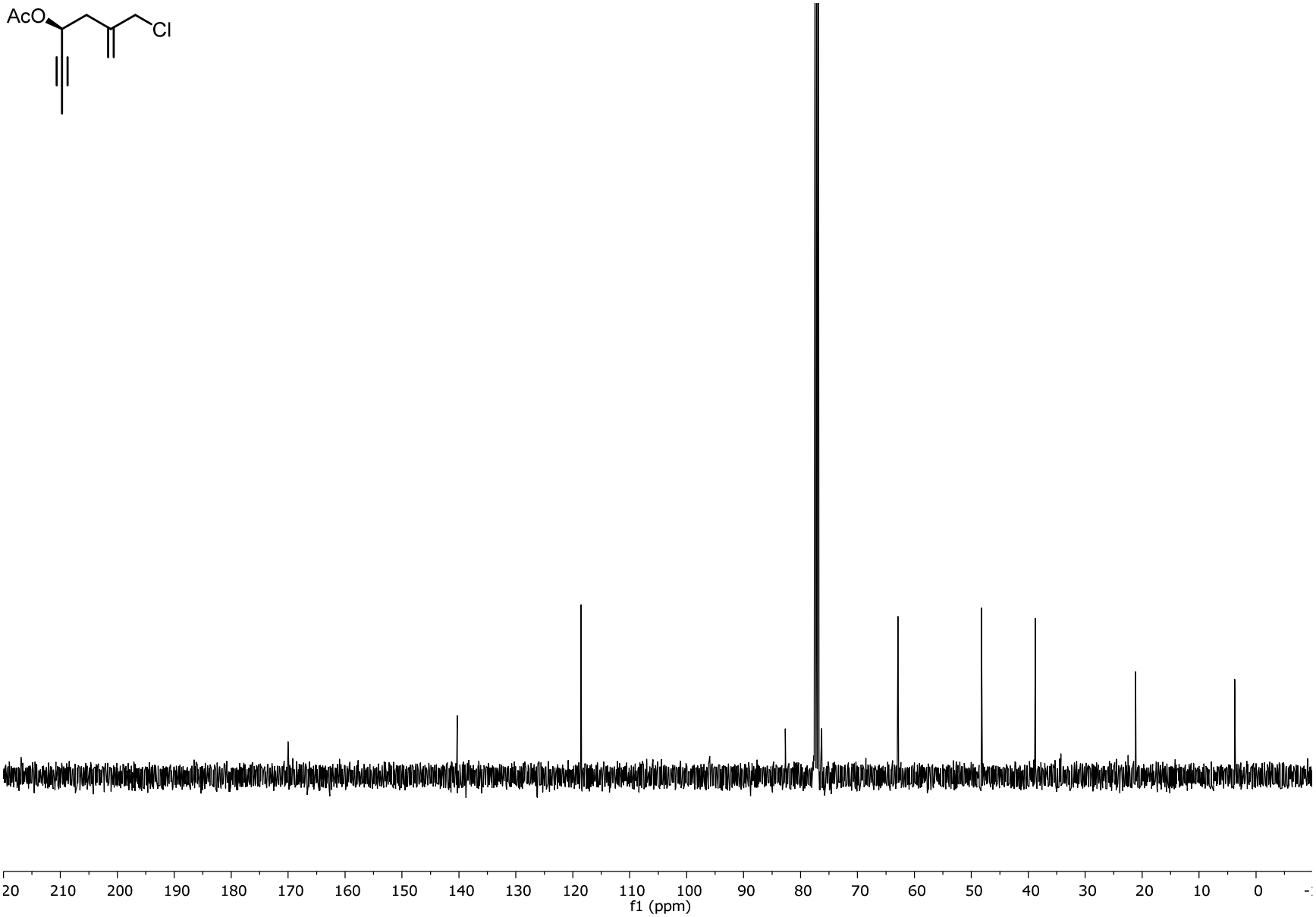
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


AcO
Cl
20
210
200
190
180
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100
90
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50
40
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10
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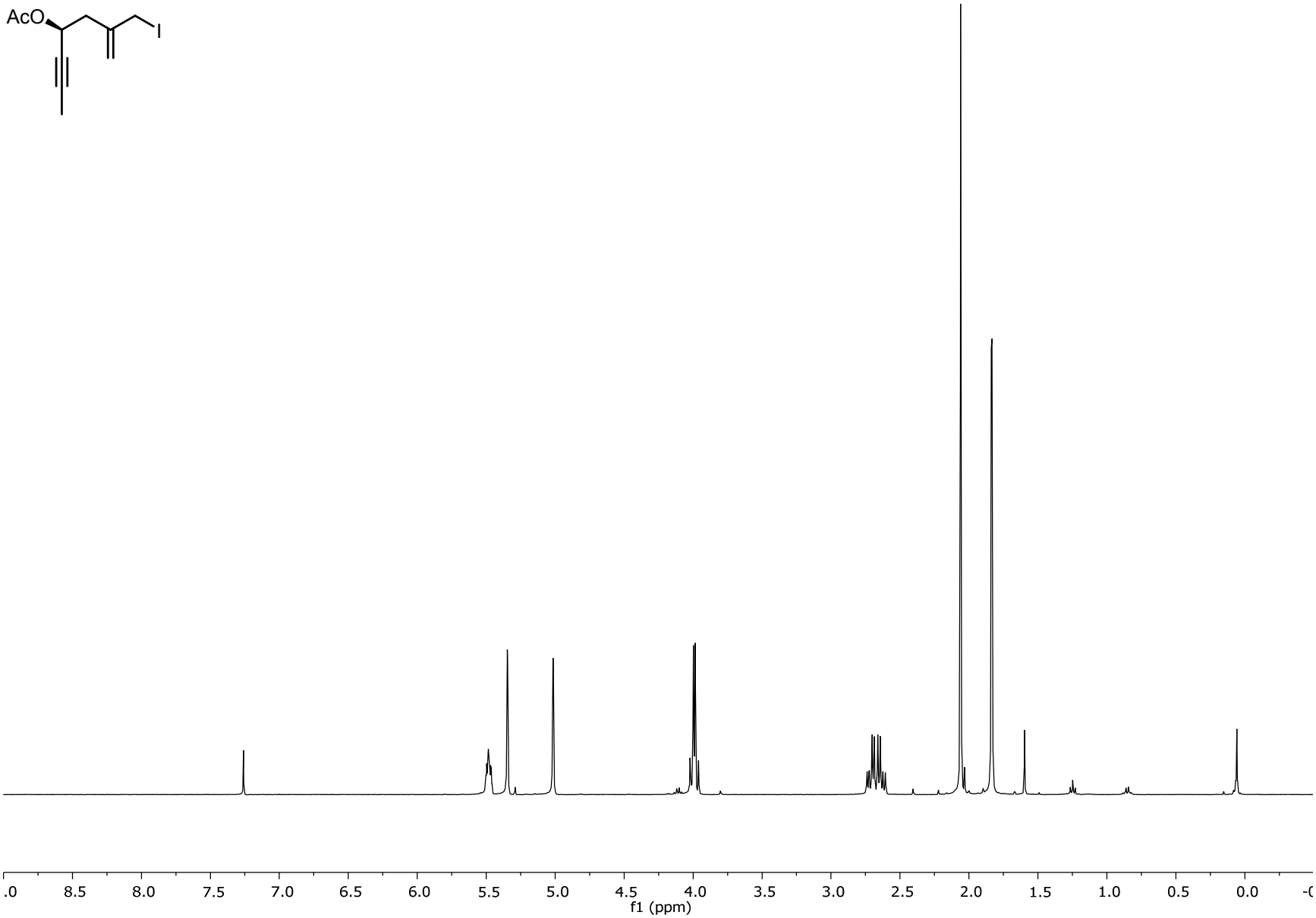
f1 (ppm)


AcO
I
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.5
3.0
2.5
2.0
1.5
1.0
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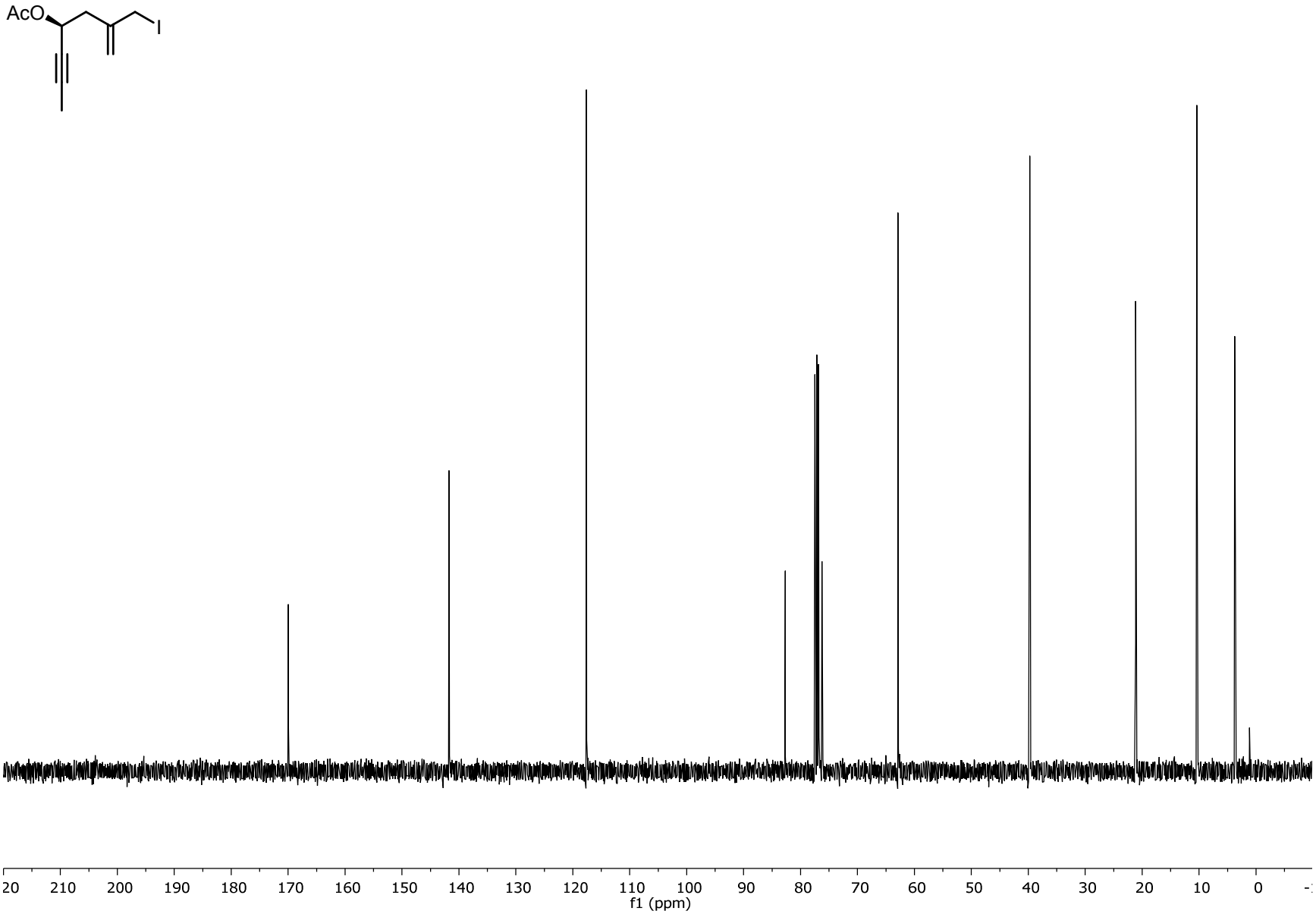
0.0
f1 (ppm)


AcO
I
220
210
200
190
180
170
160
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90
80
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50
40
30
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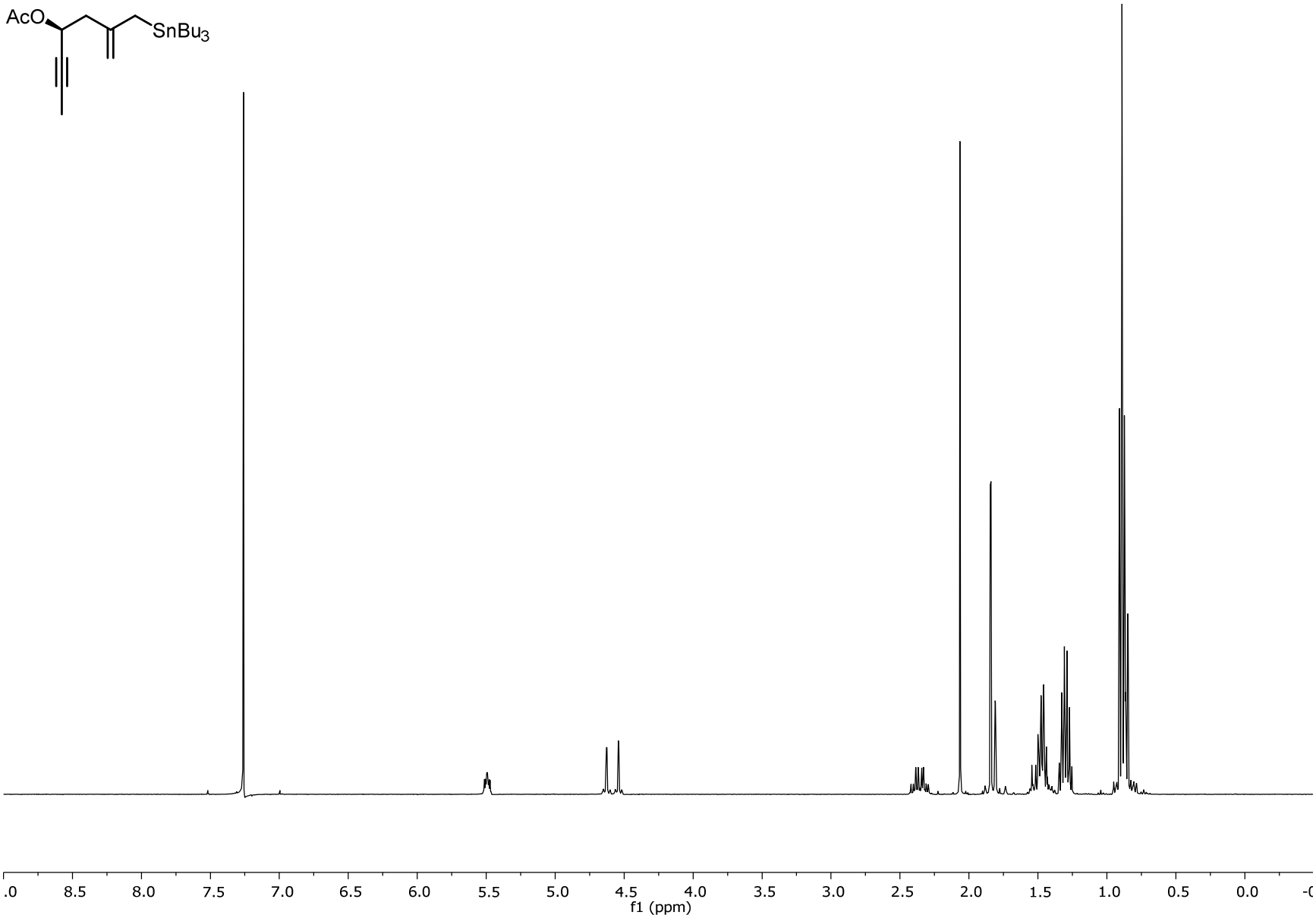
10
0
f1 (ppm)


AcO
SnBu3
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8.0
7.5
7.0
6.5
6.0
5.5
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4.5
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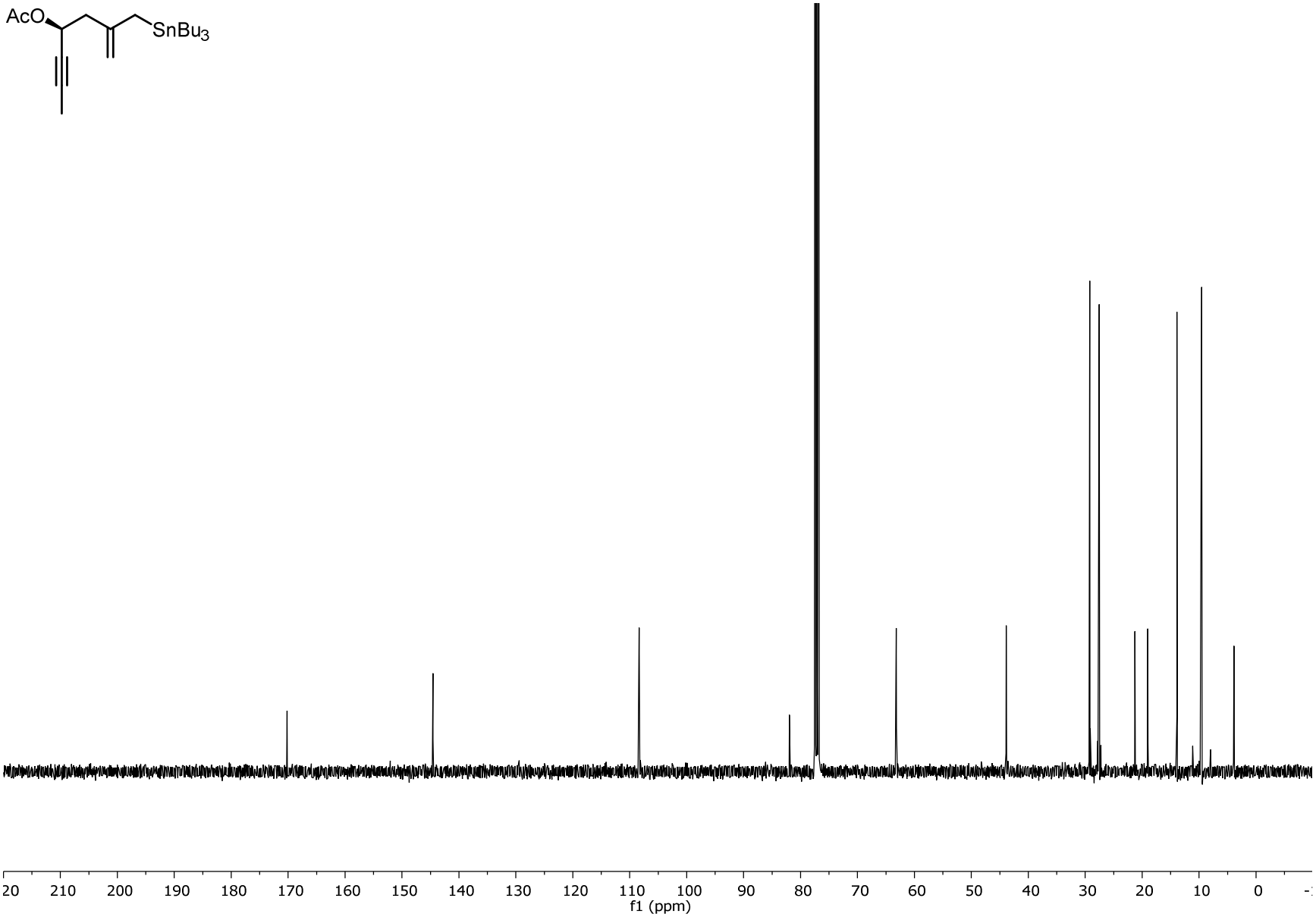
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


AcO
SnBu3
220
210
200
190
180
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130
120
110
100
90
80
70
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50
40
30
20
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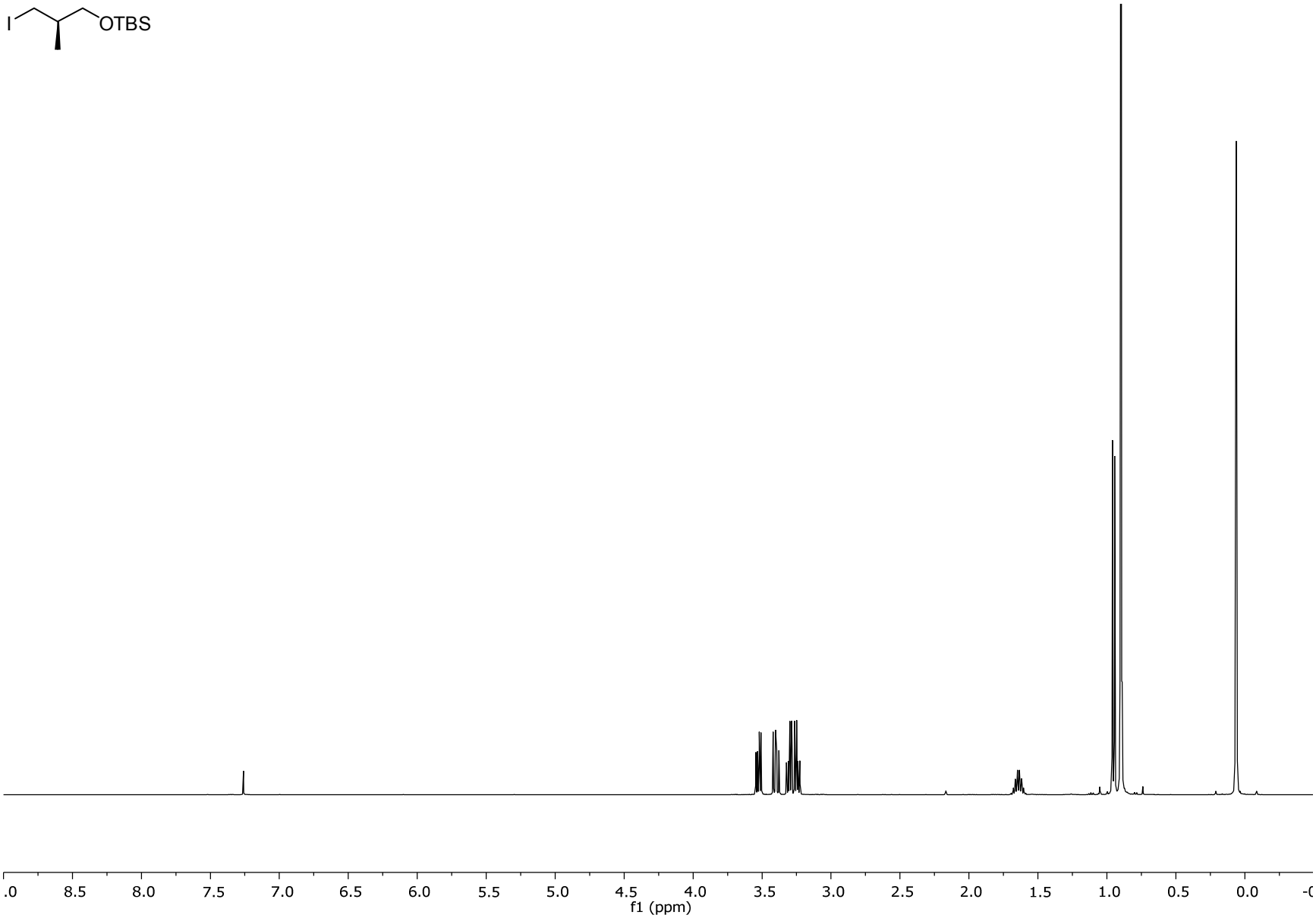
0
f1 (ppm)


I
OTBS
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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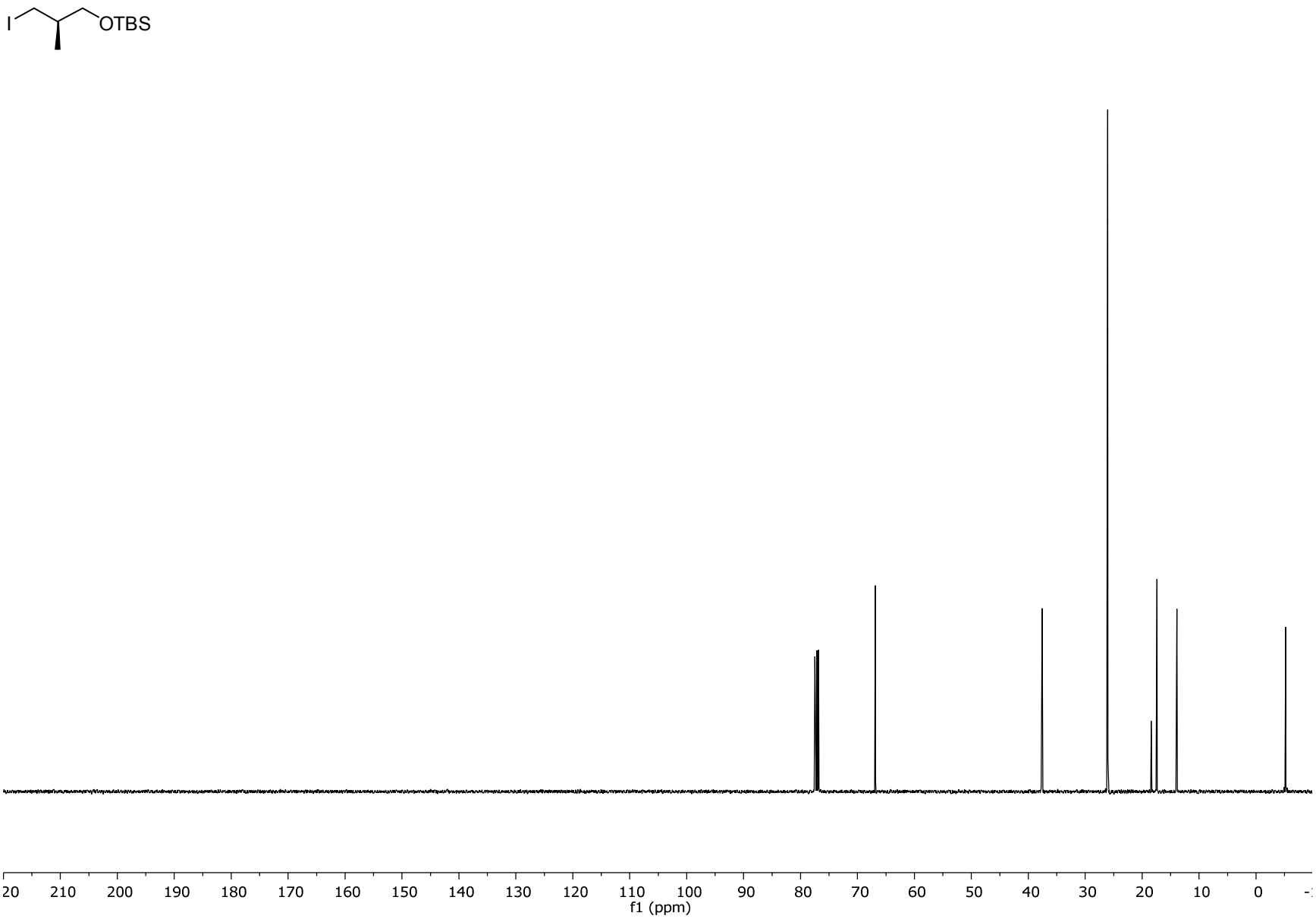
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


I
OTBS
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
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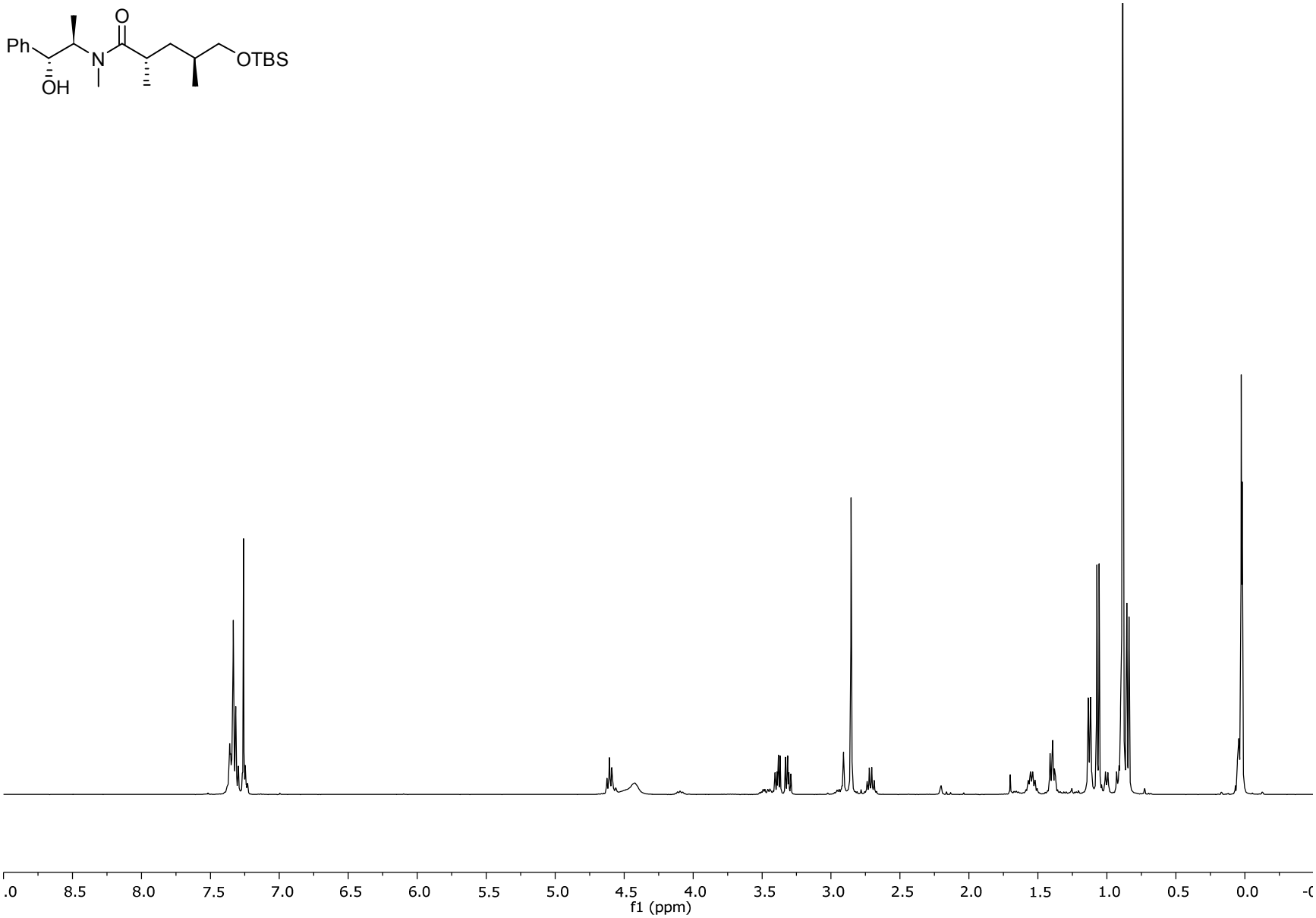
50
40
30
20
10
0
f1 (ppm)


Ph
OH
N
O
OTBS
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8.0
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6.5
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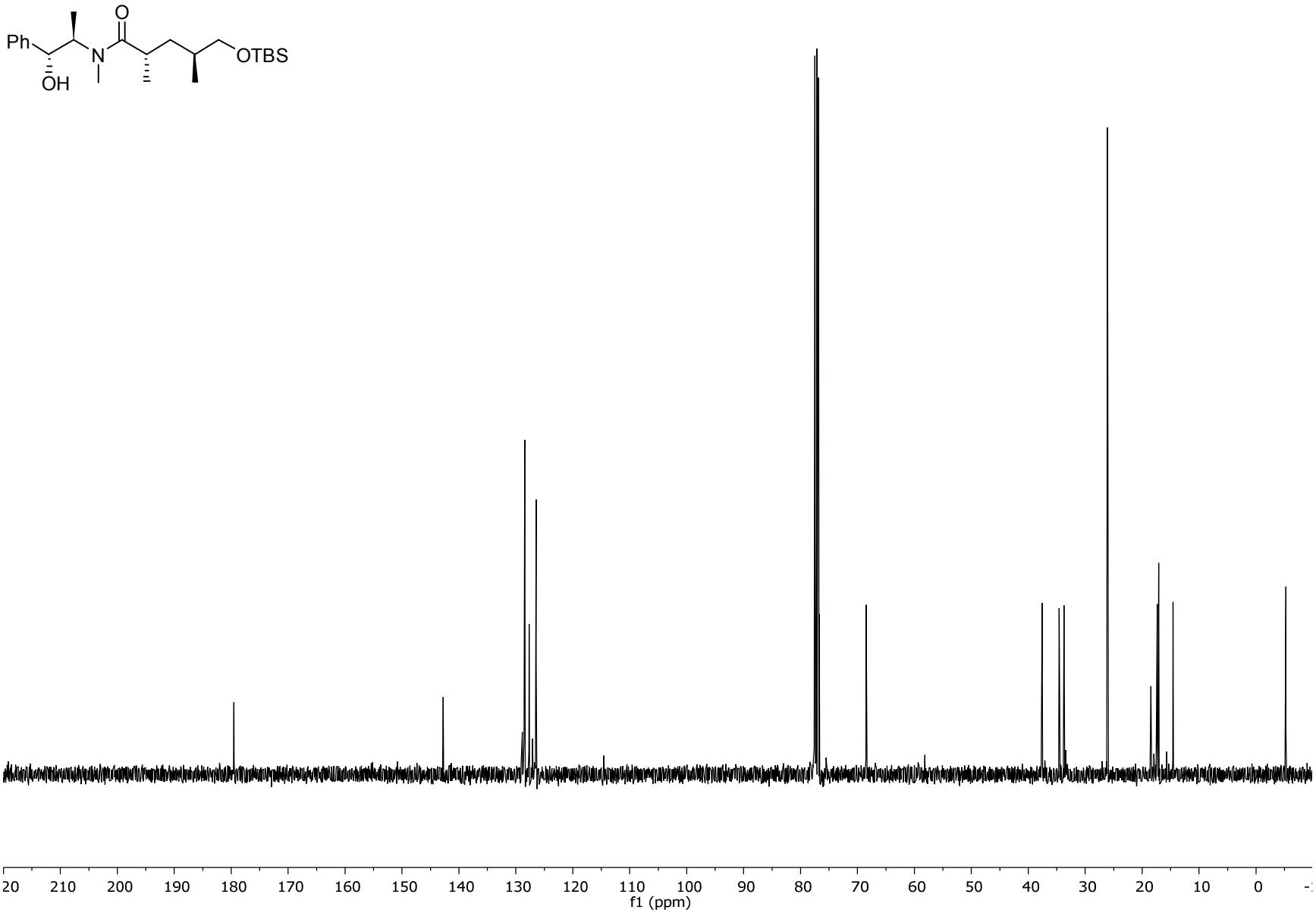
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Ph
OH
N
O
OTBS
220
210
200
190
180
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130
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110
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90
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50
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30
20
10
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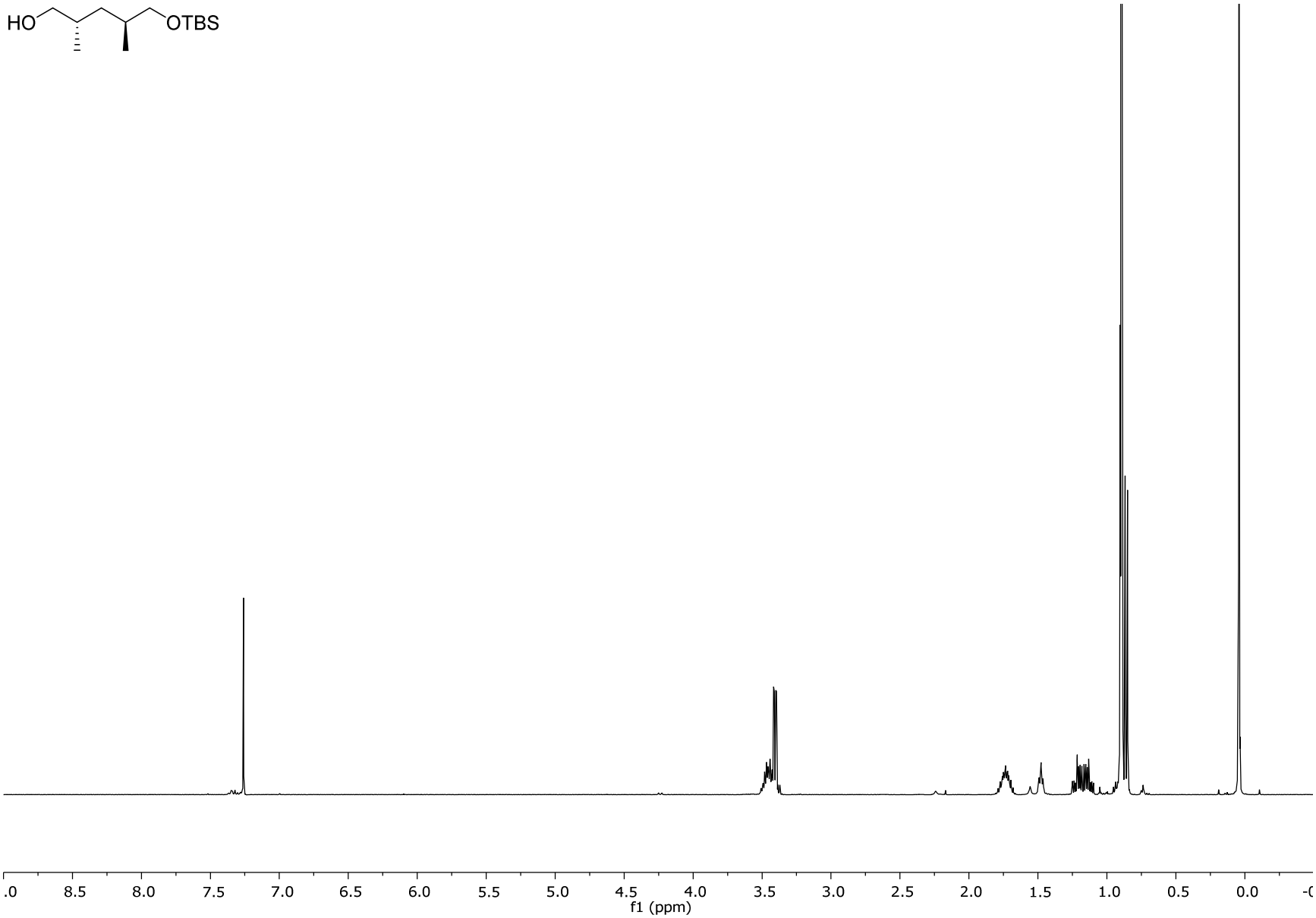
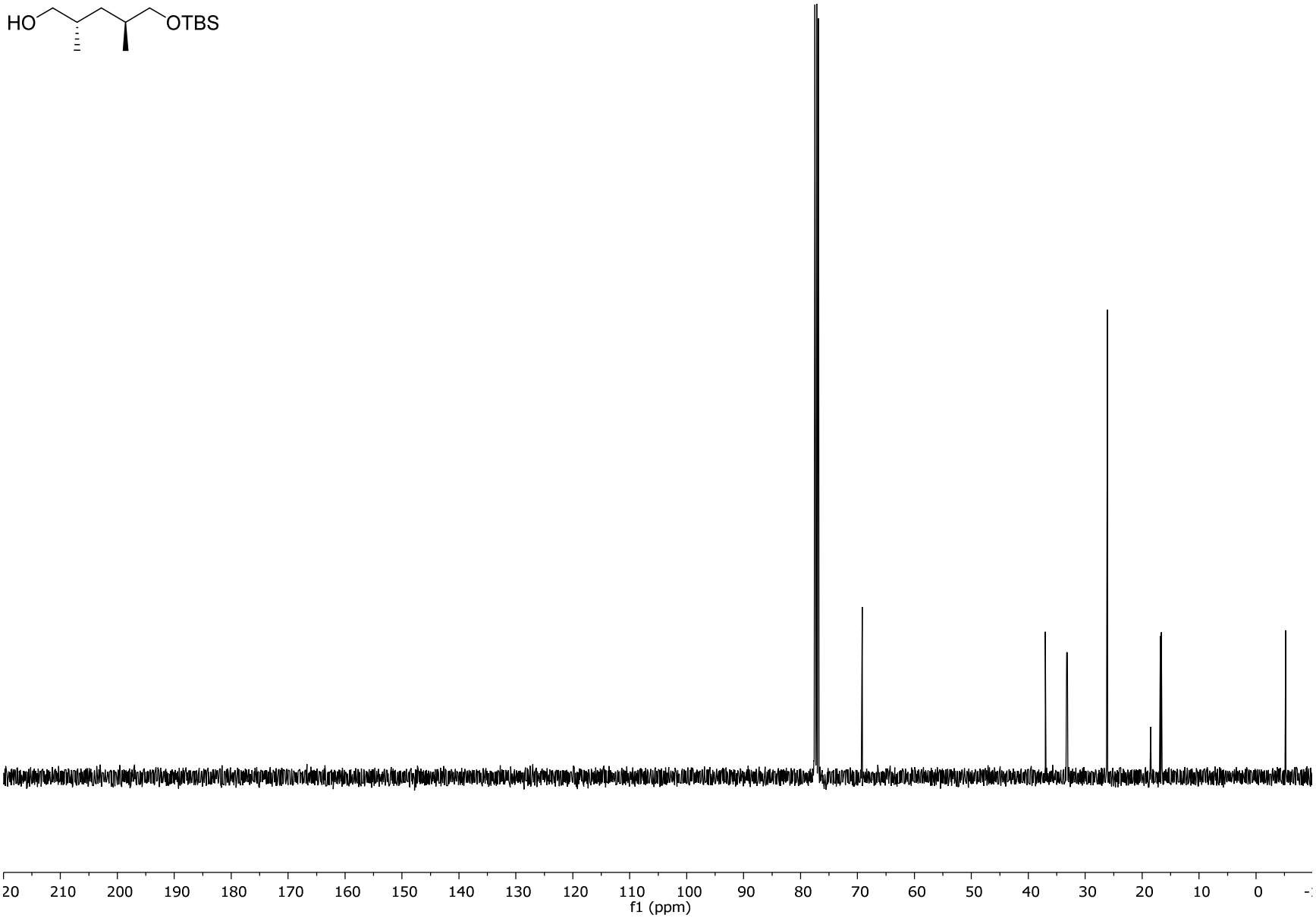
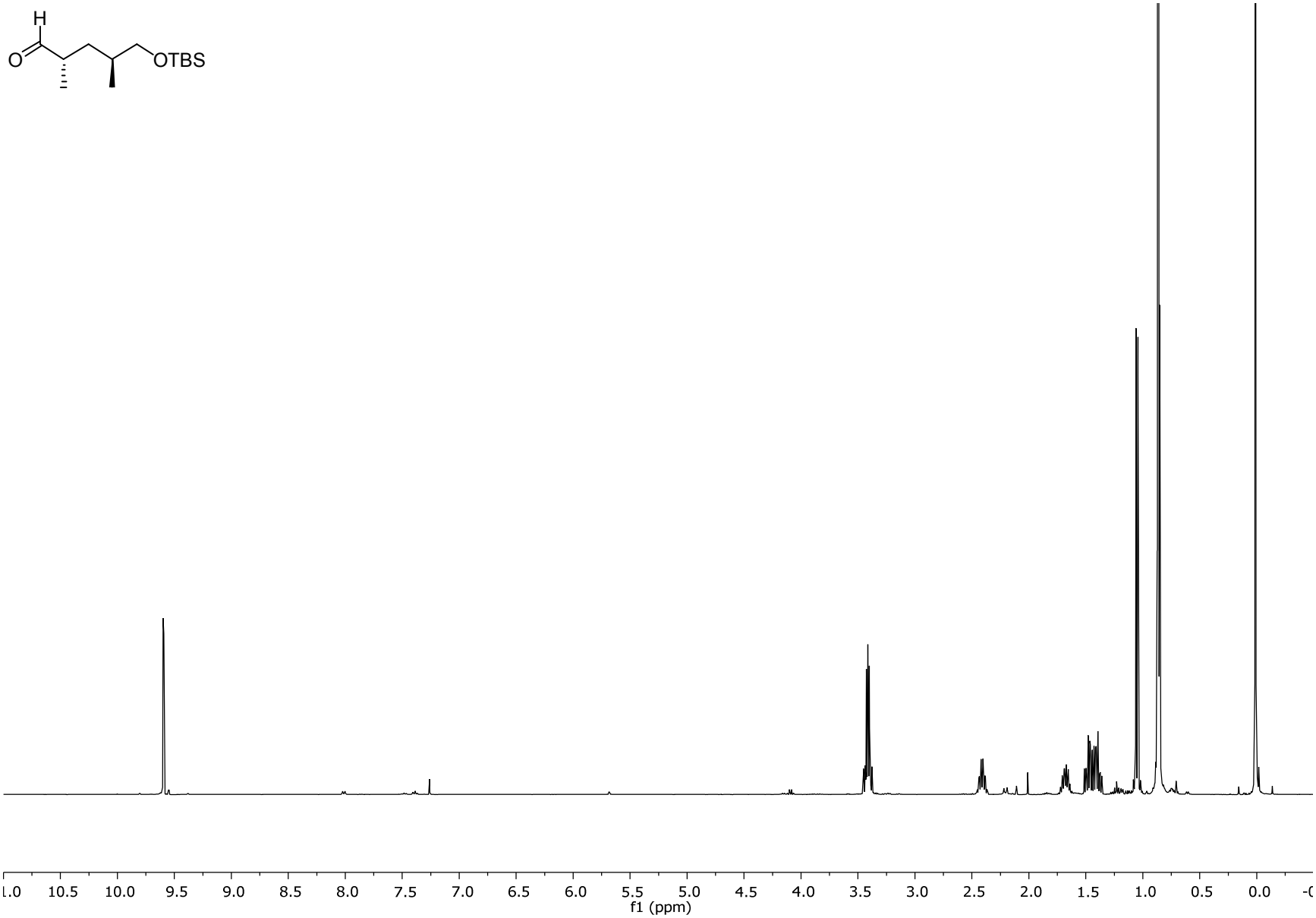
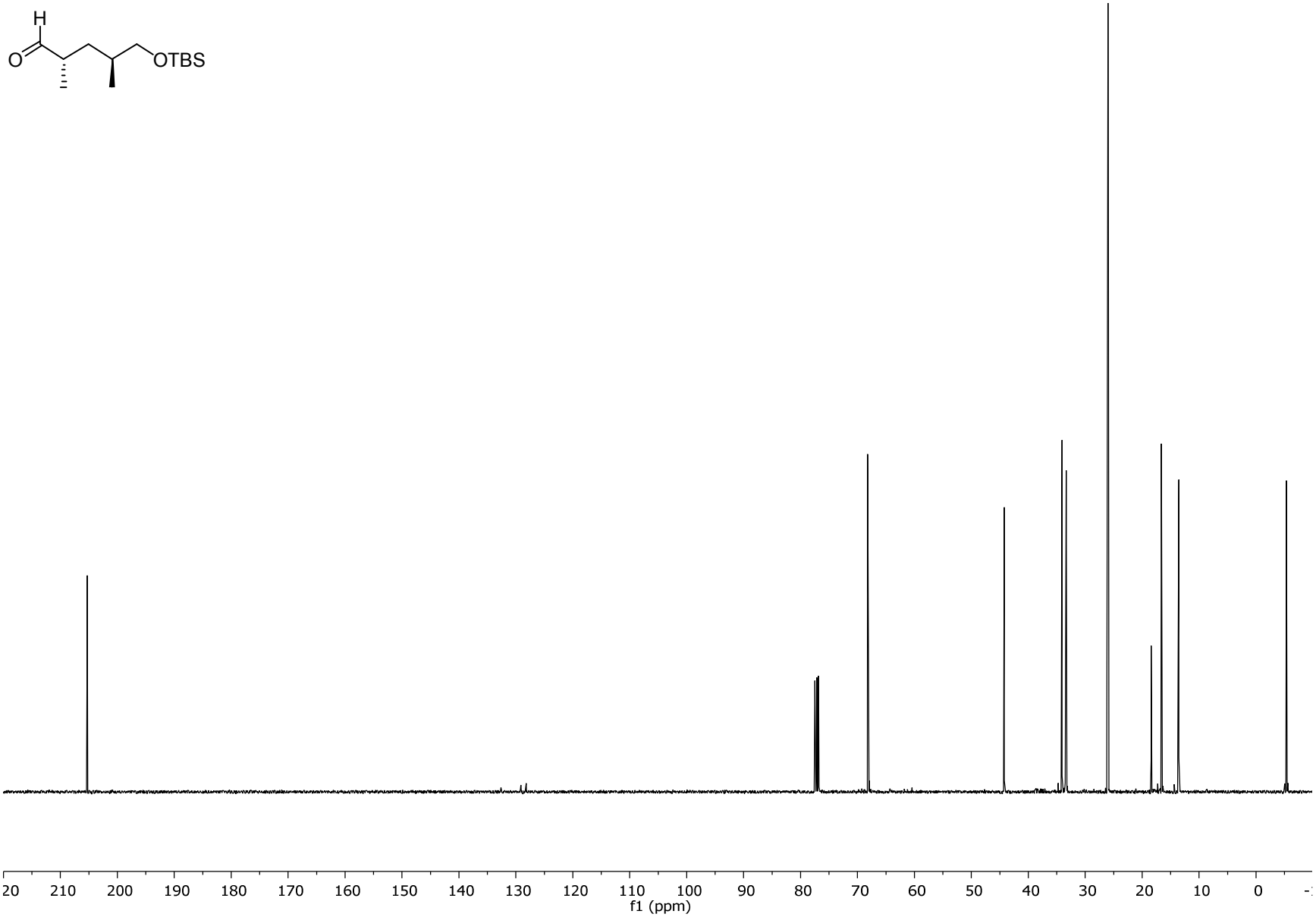
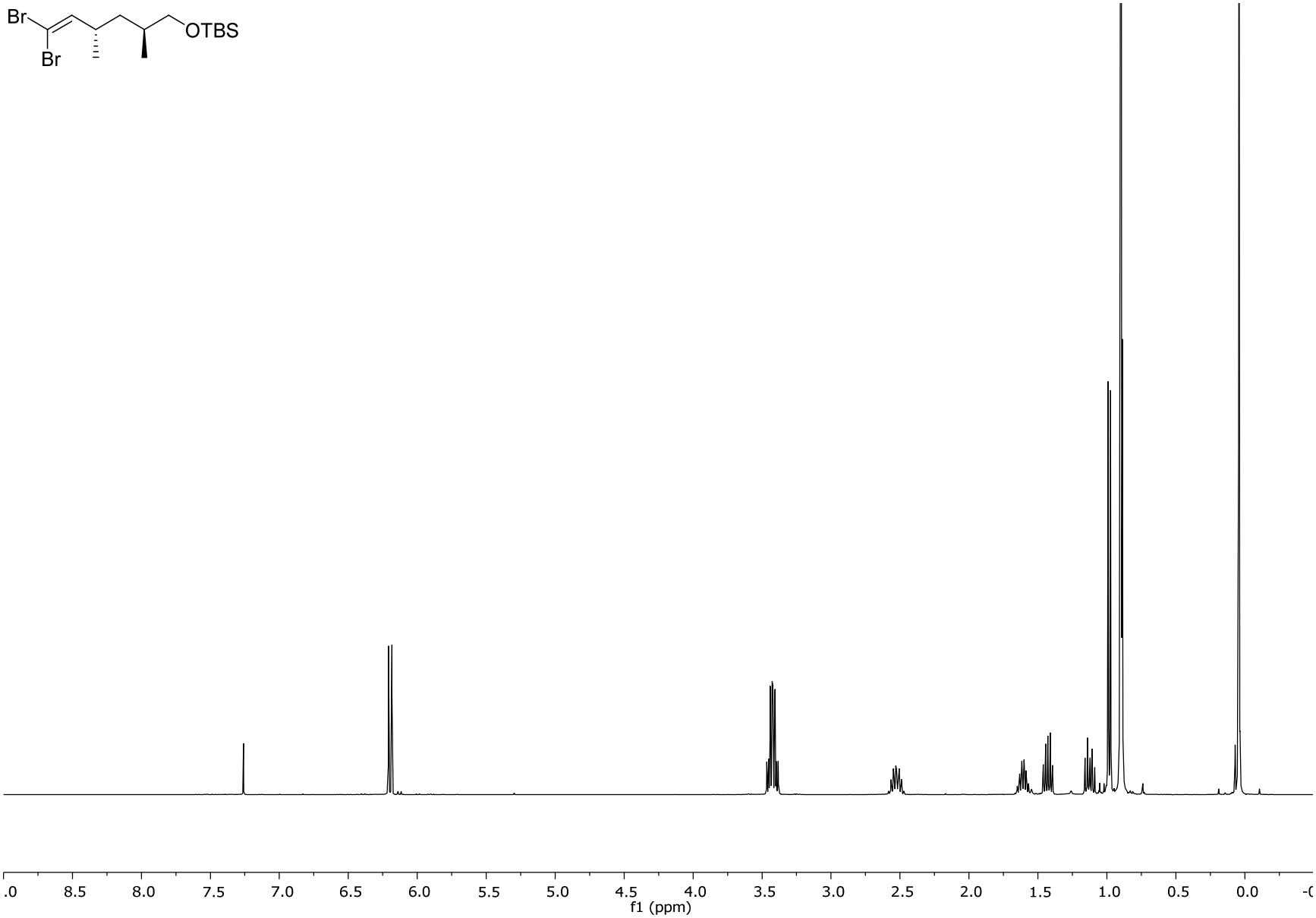
f1 (ppm)

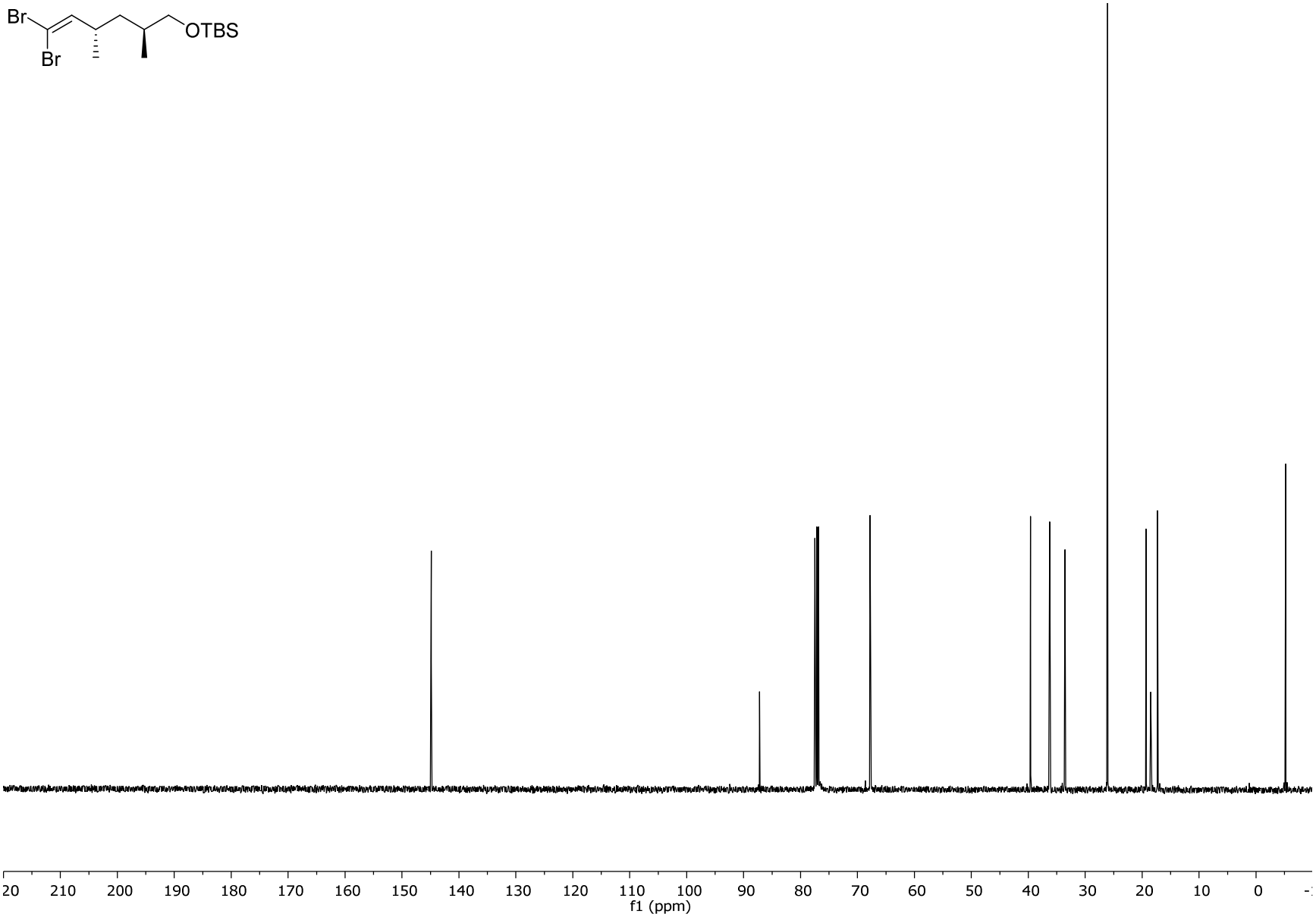

HO
OTBS
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

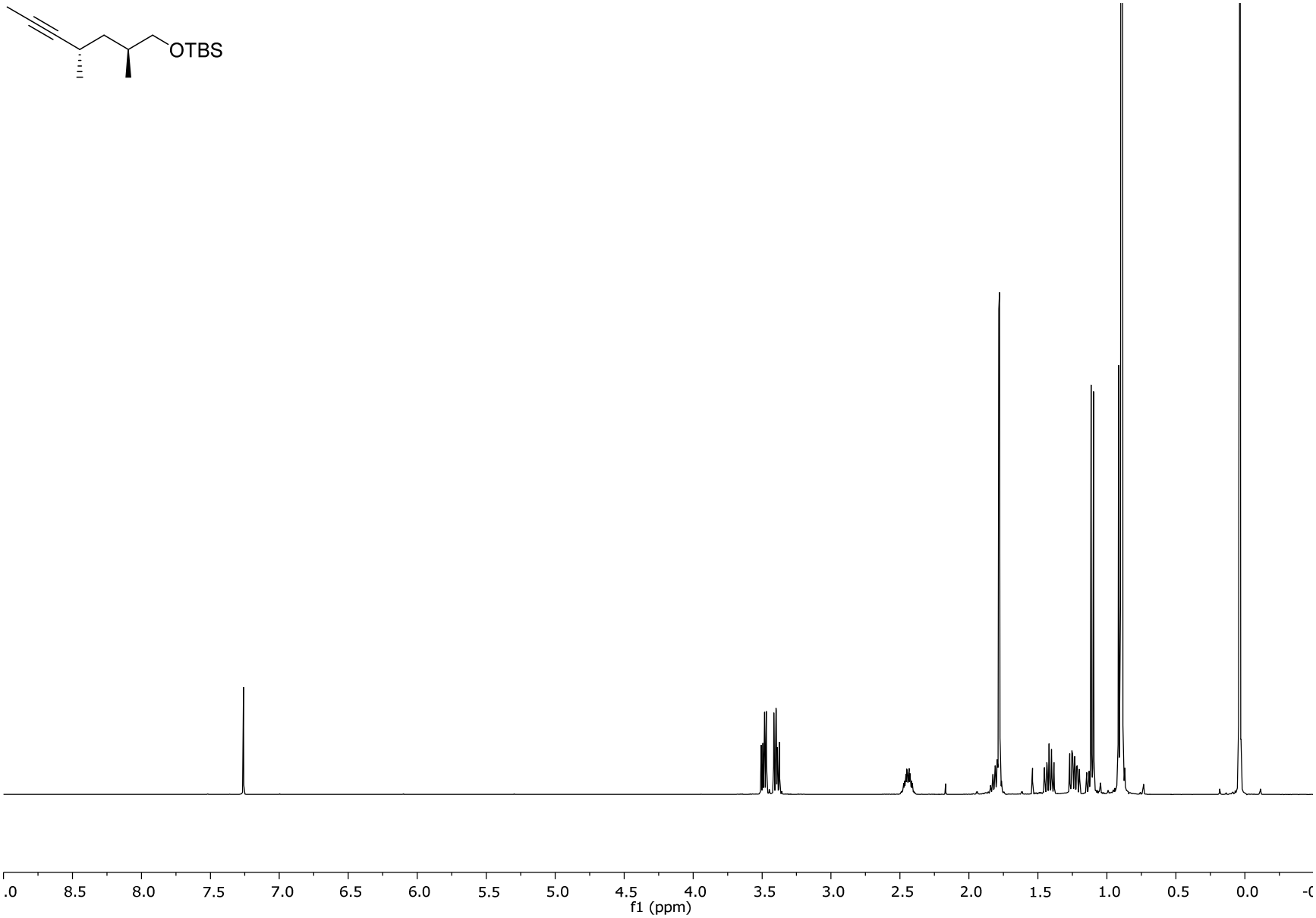

HO
OTBS
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

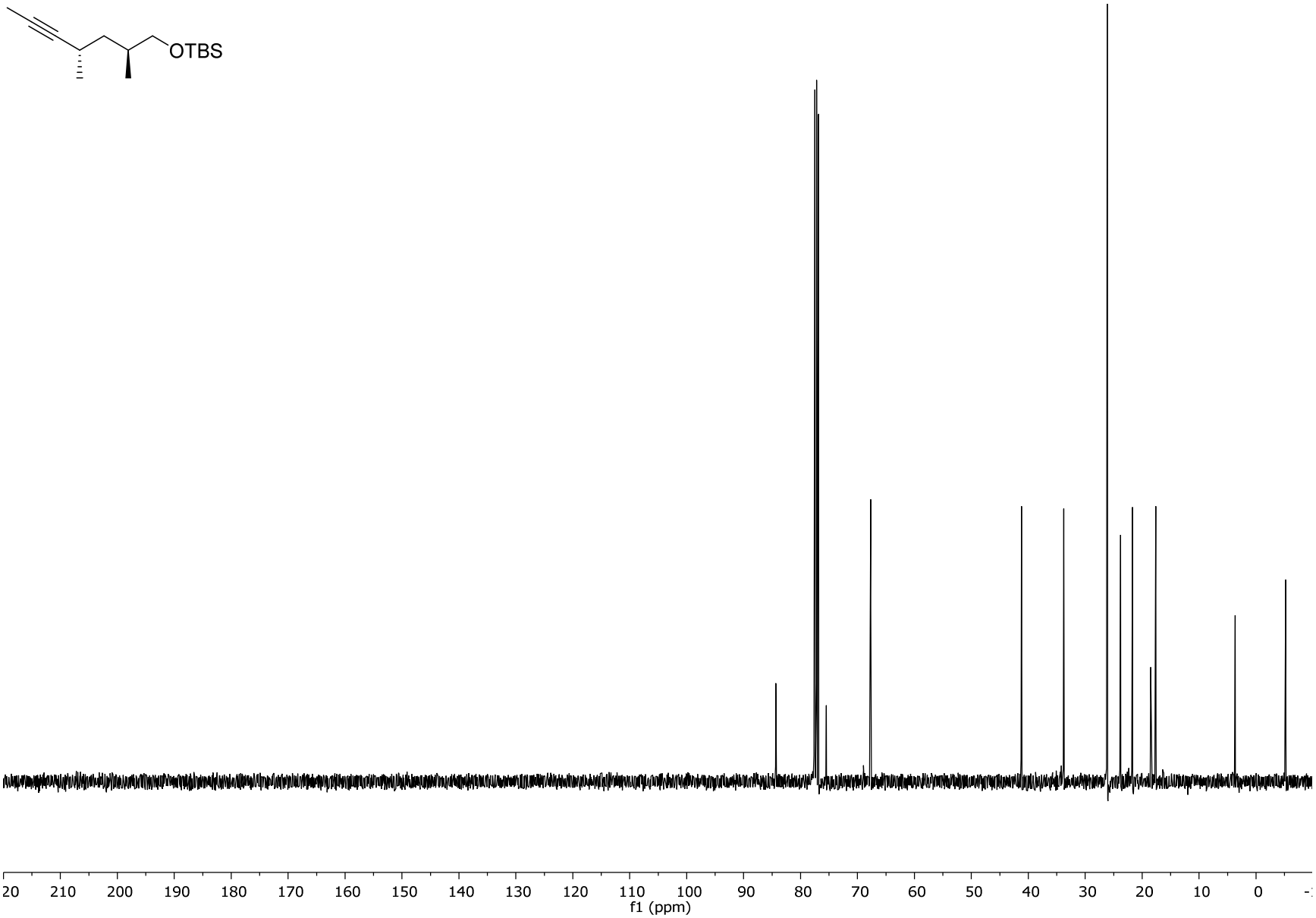

H
O
OTBS
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


H
O
OTBS
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Br
Br
OTBS
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Br
Br
OTBS
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OTBS
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OTBS
220
210
200
190
180
170
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150
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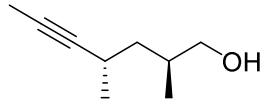
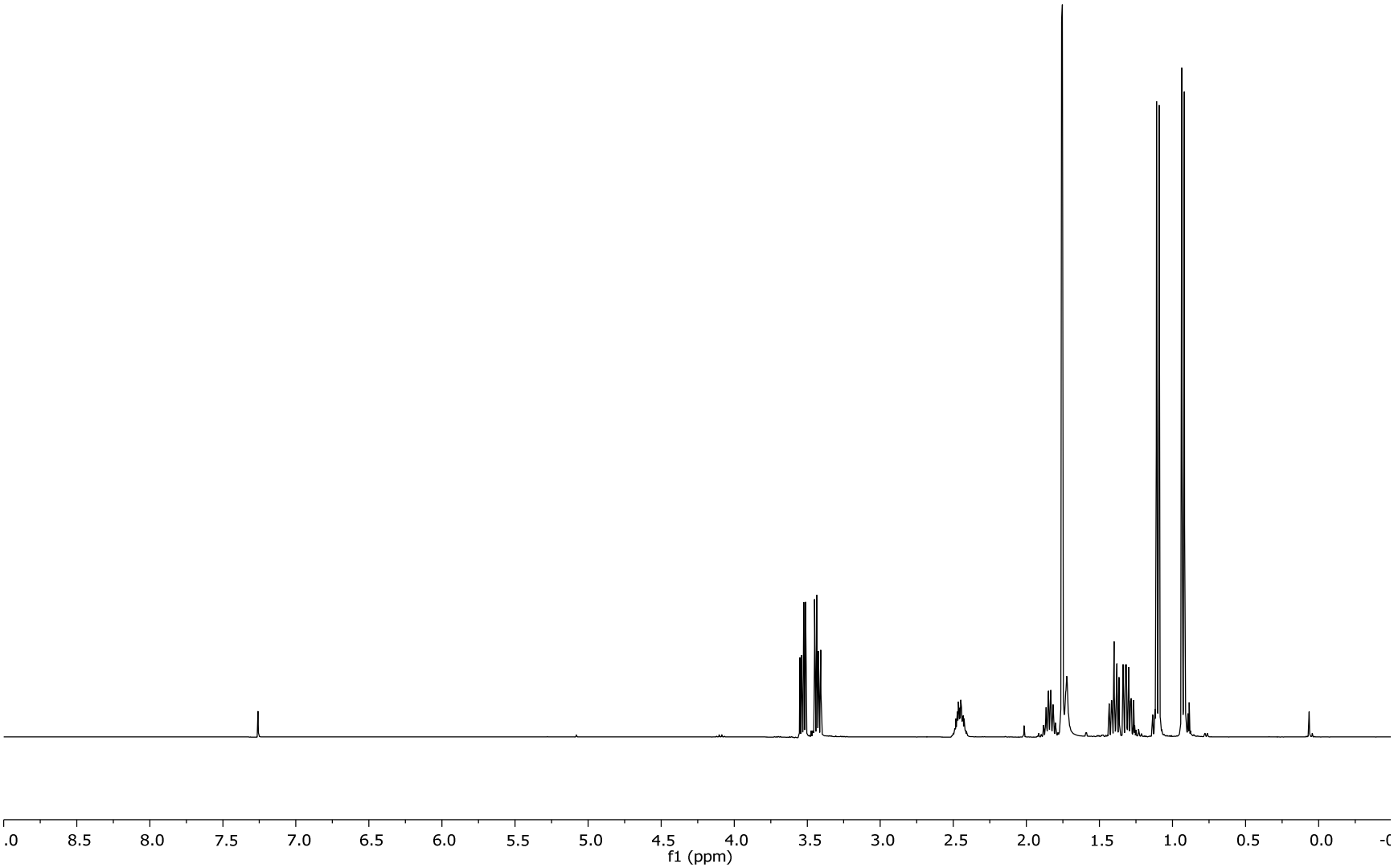
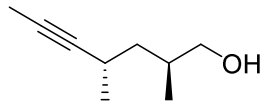
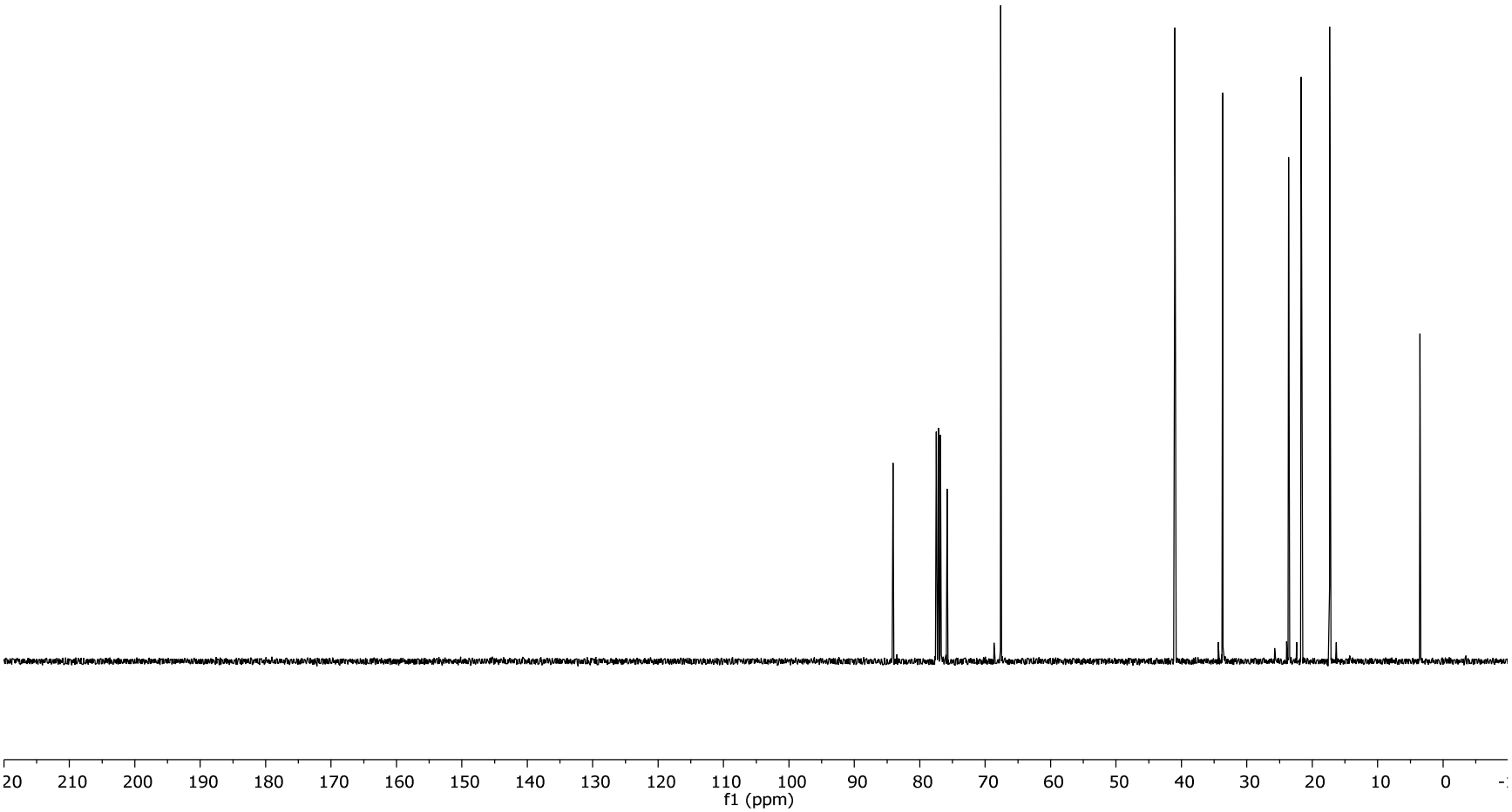
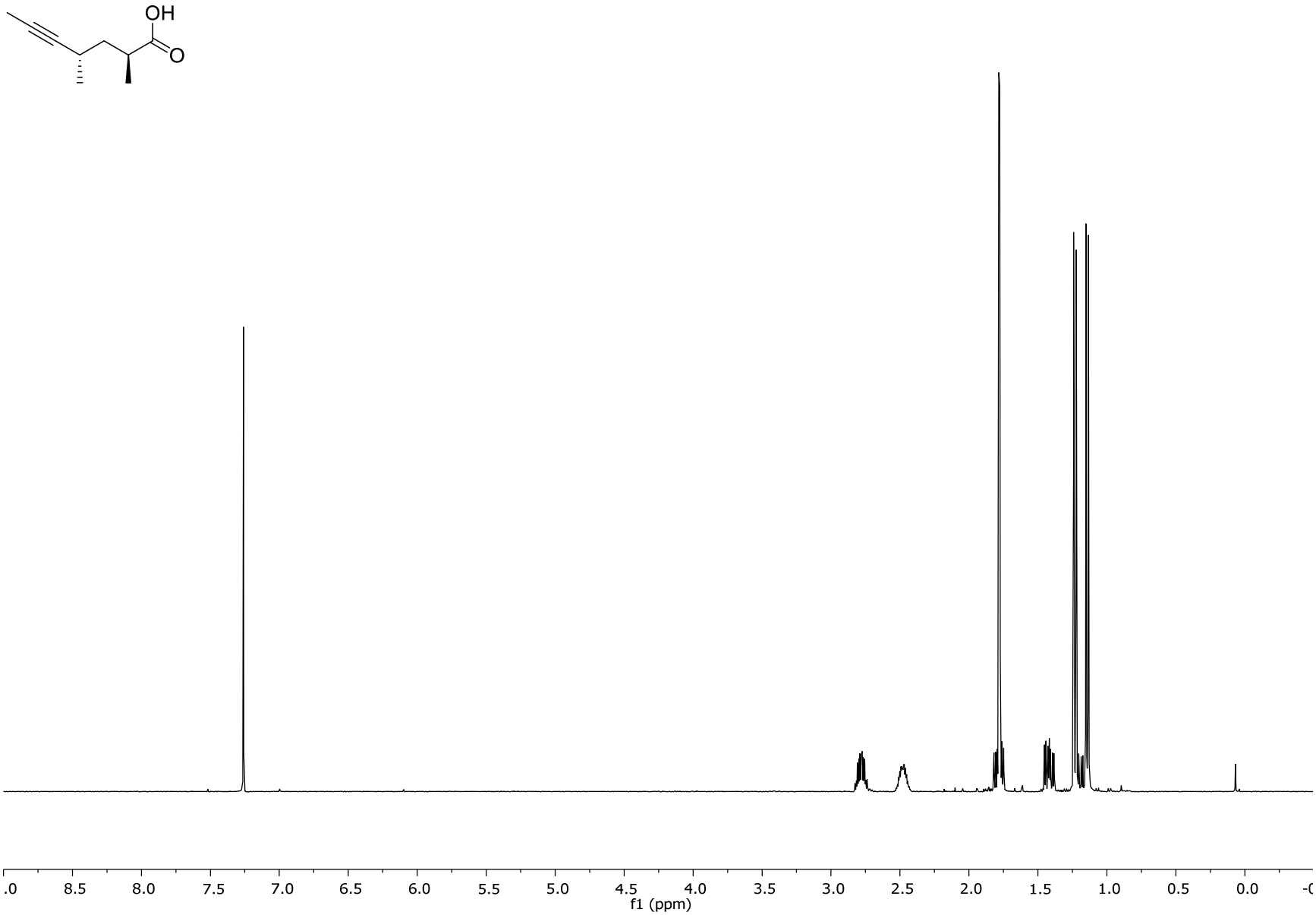
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

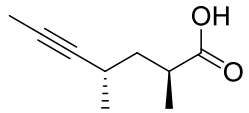

OH

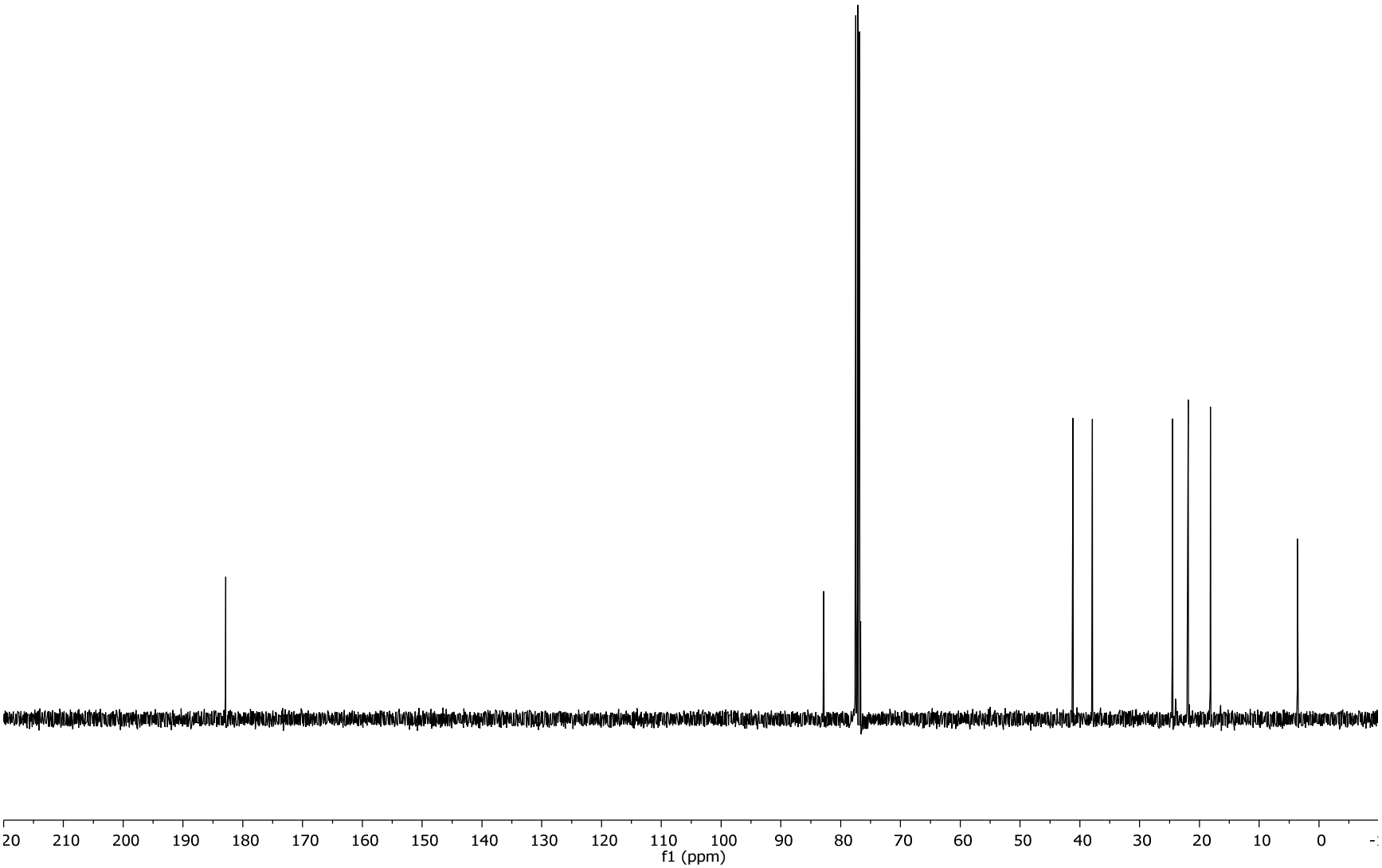

.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OH


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OH
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OH
O


220
210
200
190
180
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120
110
100
90
80
70
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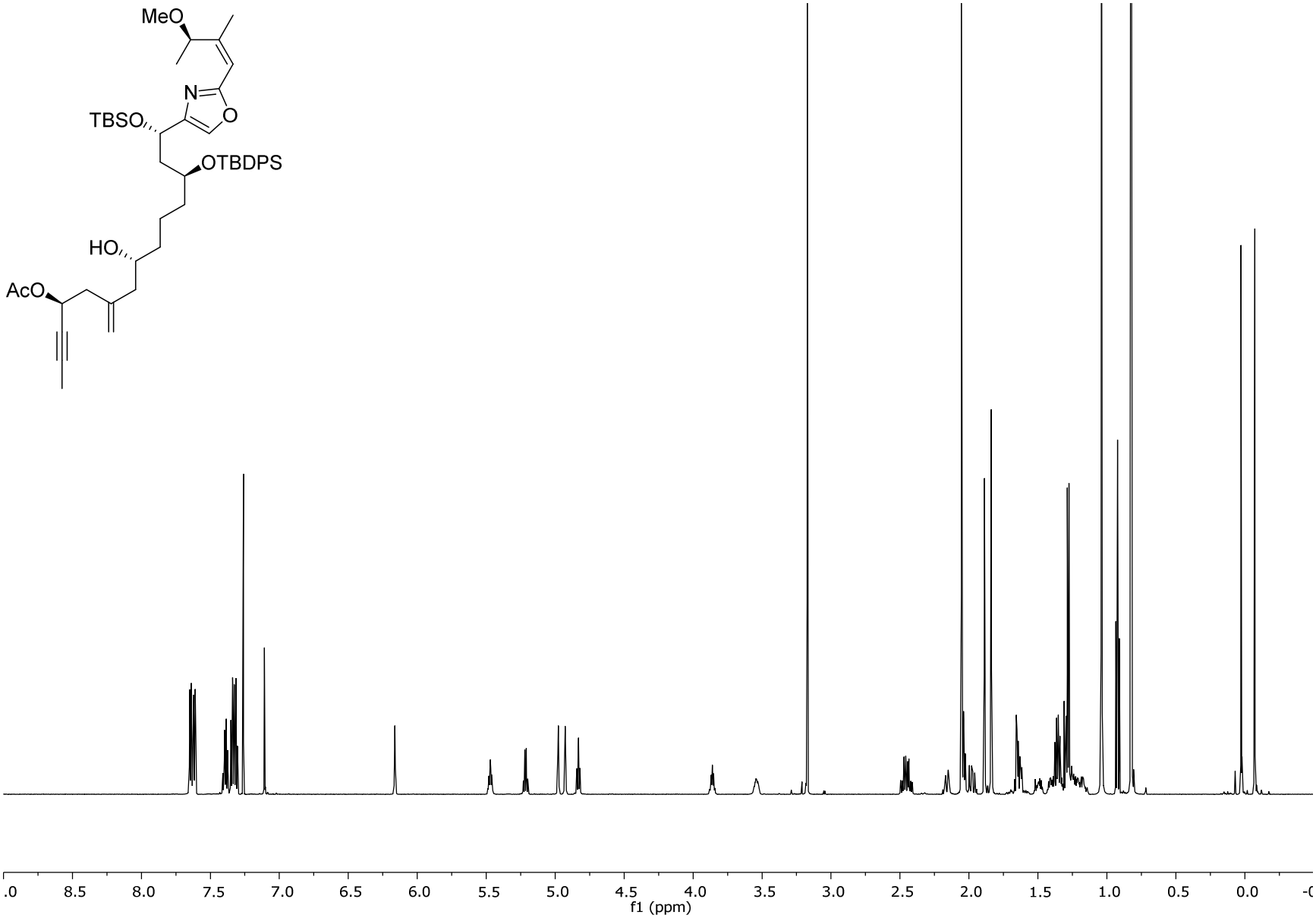
50
40
30
20
10
0
f1 (ppm)


MeO
N
O
TBSO
OTBDPS
HO
AcO
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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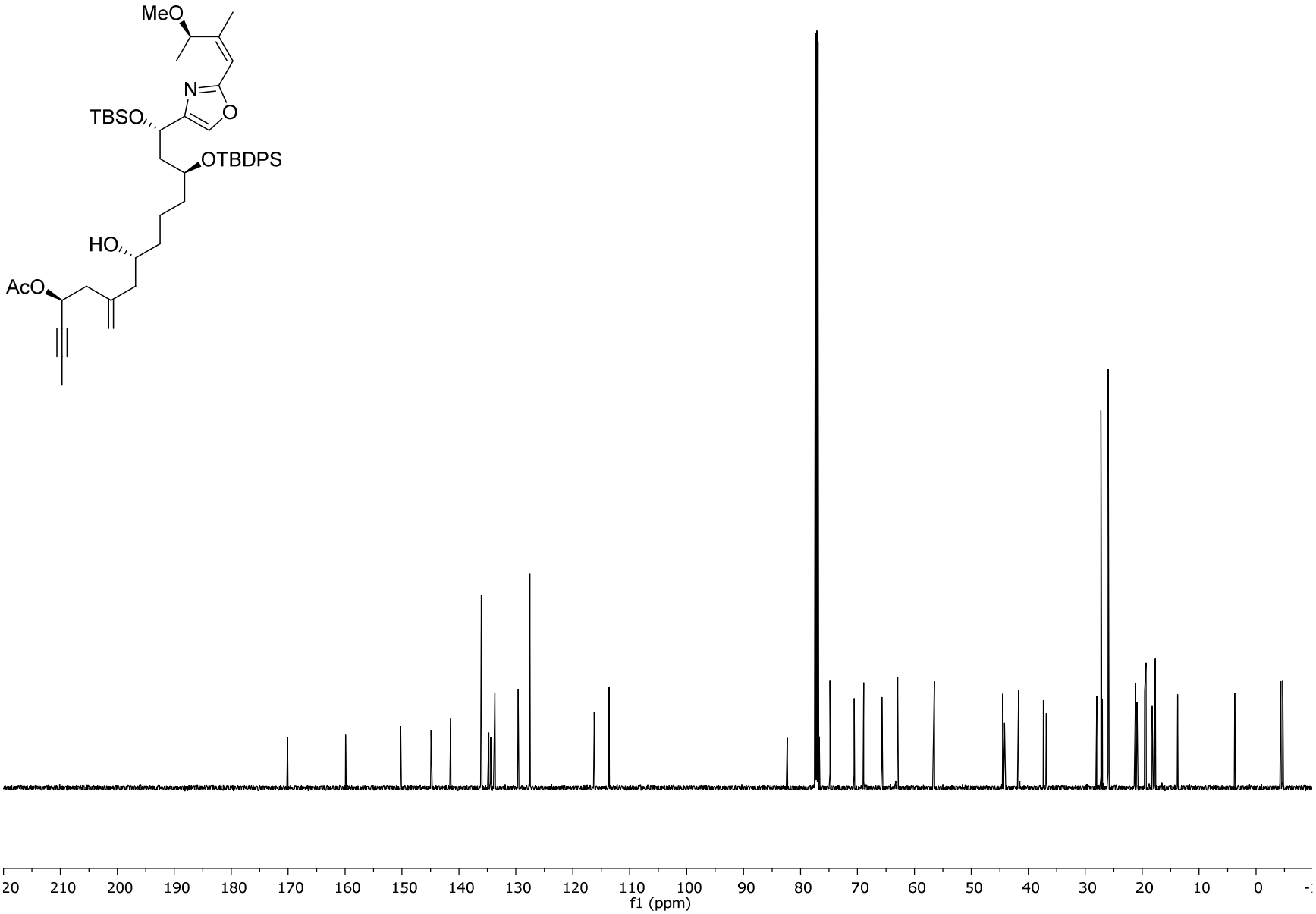
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


MeO
N
O
TBSO
OTBDPS
HO
AcO
220
210
200
190
180
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160
150
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130
120
110
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90
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70
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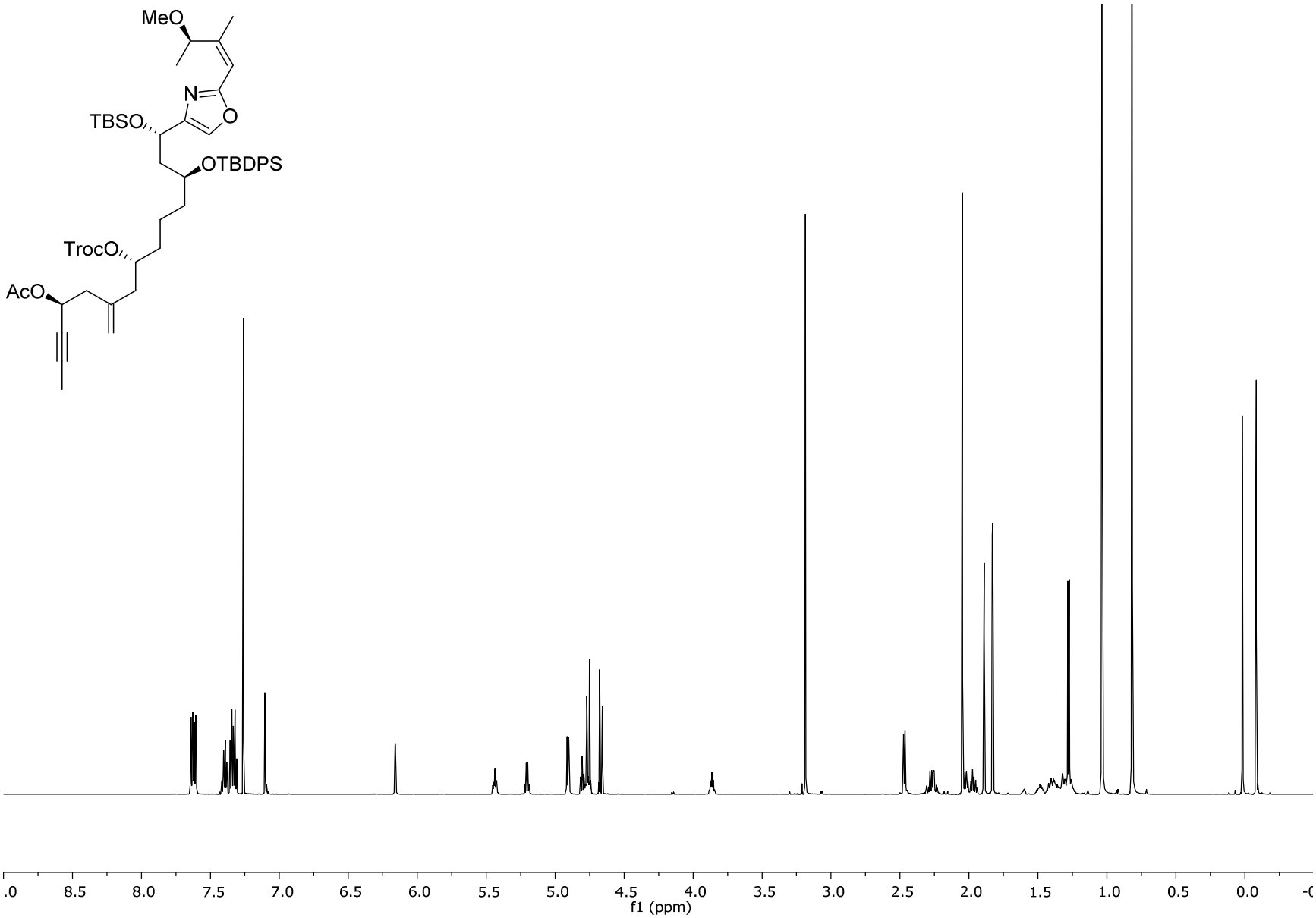
50
40
30
20
10
0
f1 (ppm)


MeO
N
O
TBSO
OTBDPS
TrocO
AcO
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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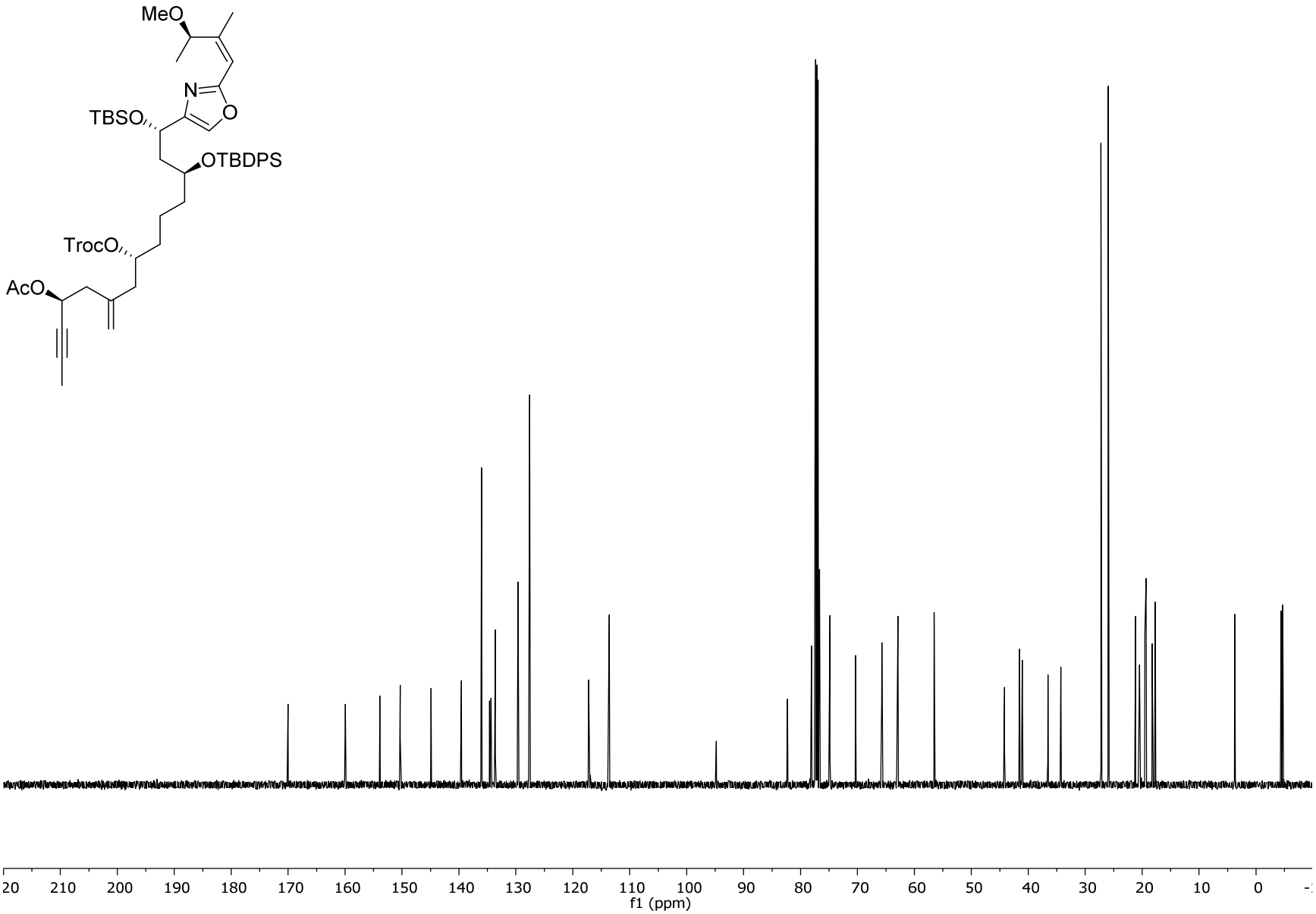
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


MeO
N
O
TBSO
OTBDPS
TrocO
AcO
220
210
200
190
180
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90
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70
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50
40
30
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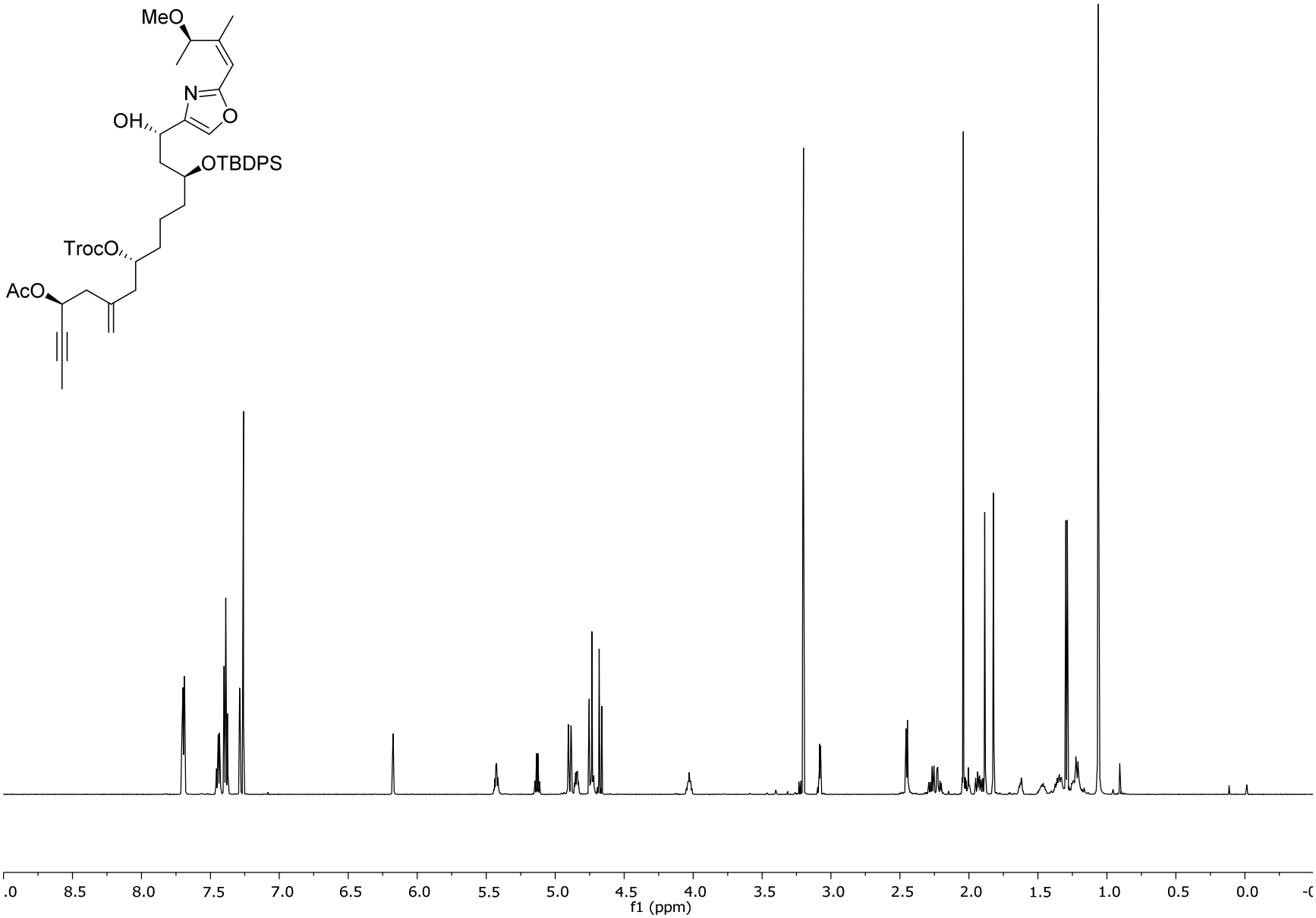
10
0
f1 (ppm)


MeO
N
O
OH
OTBDPS
TrocO
AcO
.0
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8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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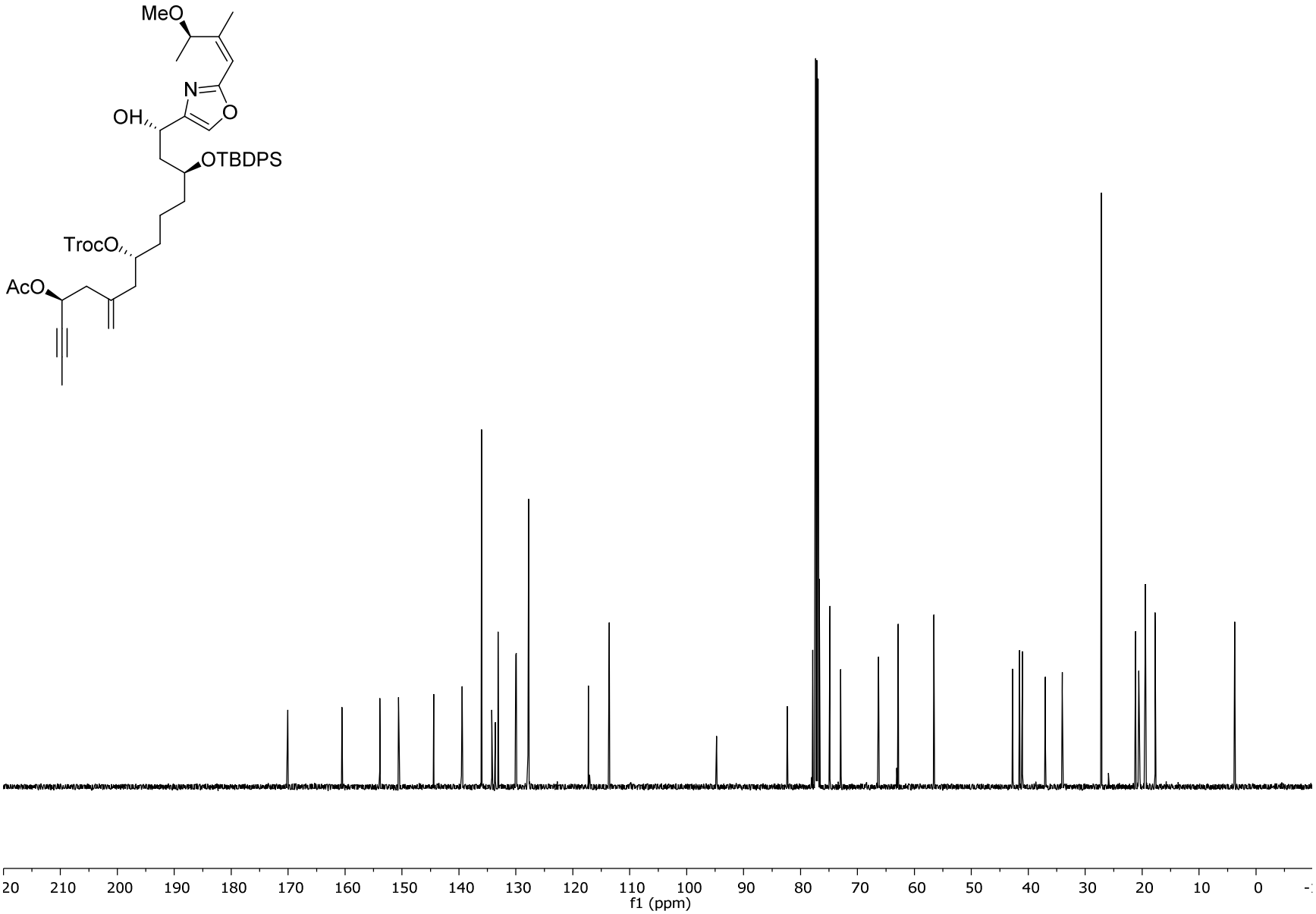
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


MeO
N
O
OH
OTBDPS
TrocO
AcO
220
210
200
190
180
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50
40
30
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10
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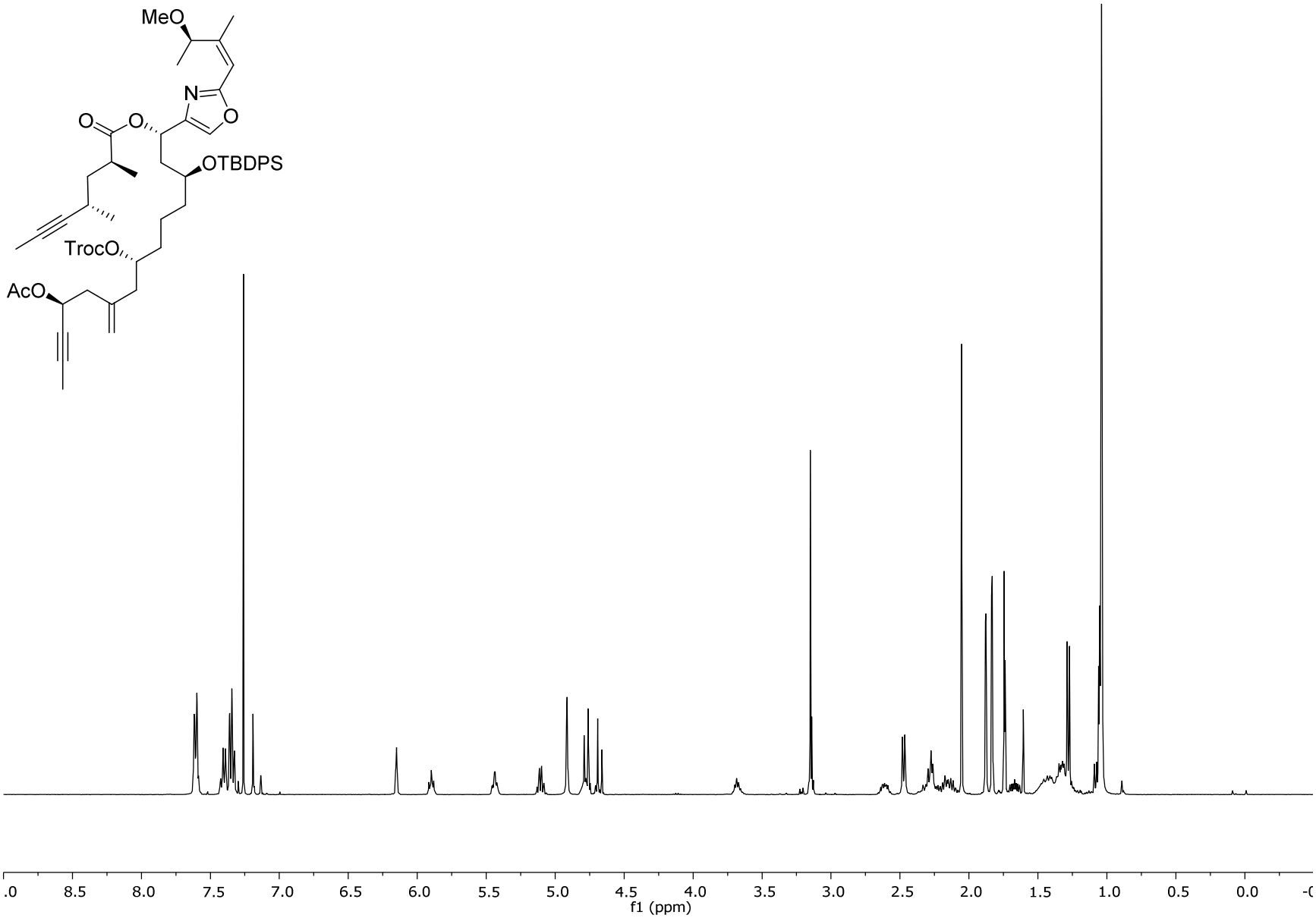
f1 (ppm)


MeO
N
O
O
O
OTBDPS
TrocO
AcO
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.0
2.5
2.0
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1.0
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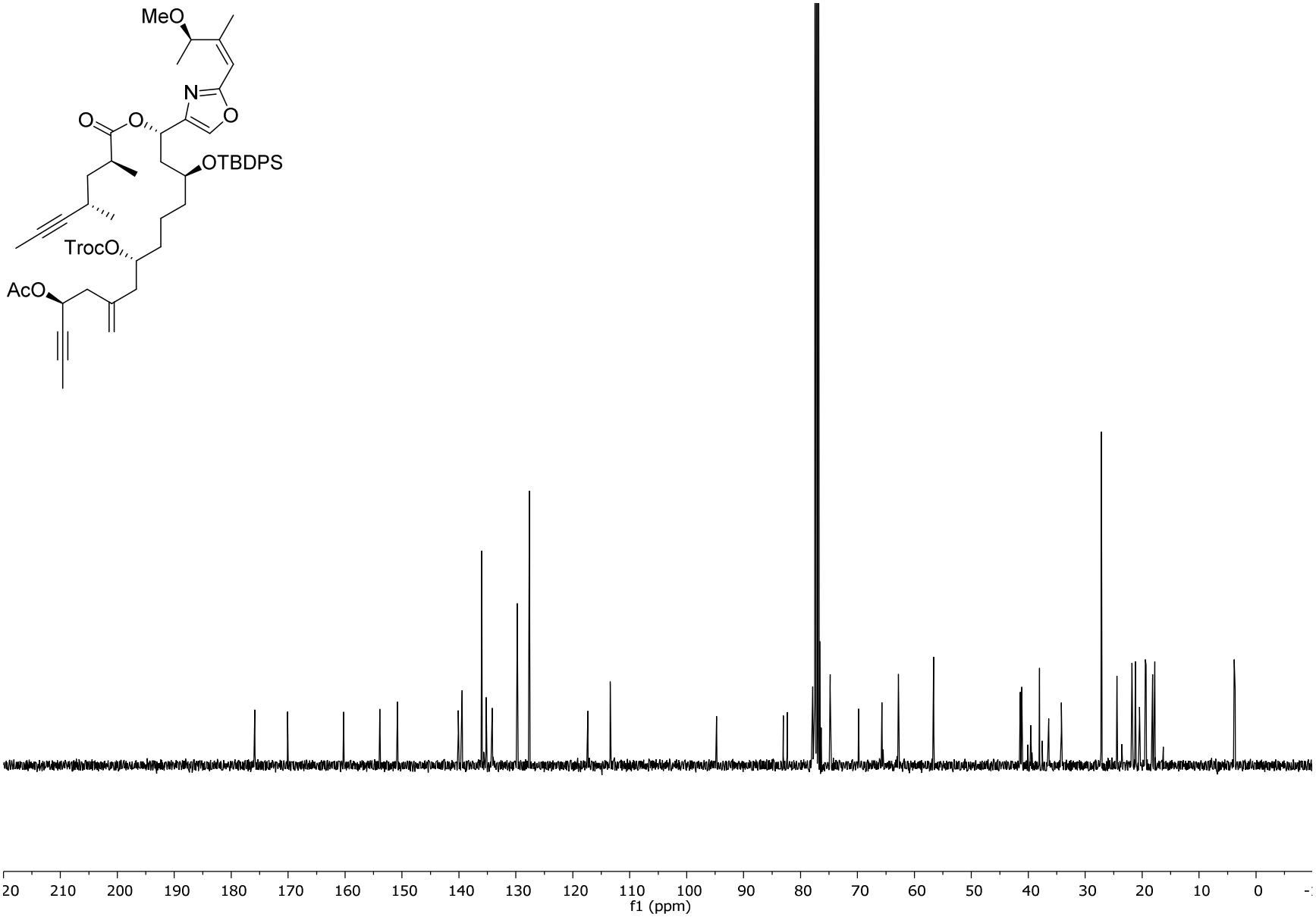
0.0
f1 (ppm)


MeO
N
O
O
O
OTBDPS
TrocO
AcO
220
210
200
190
180
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120
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90
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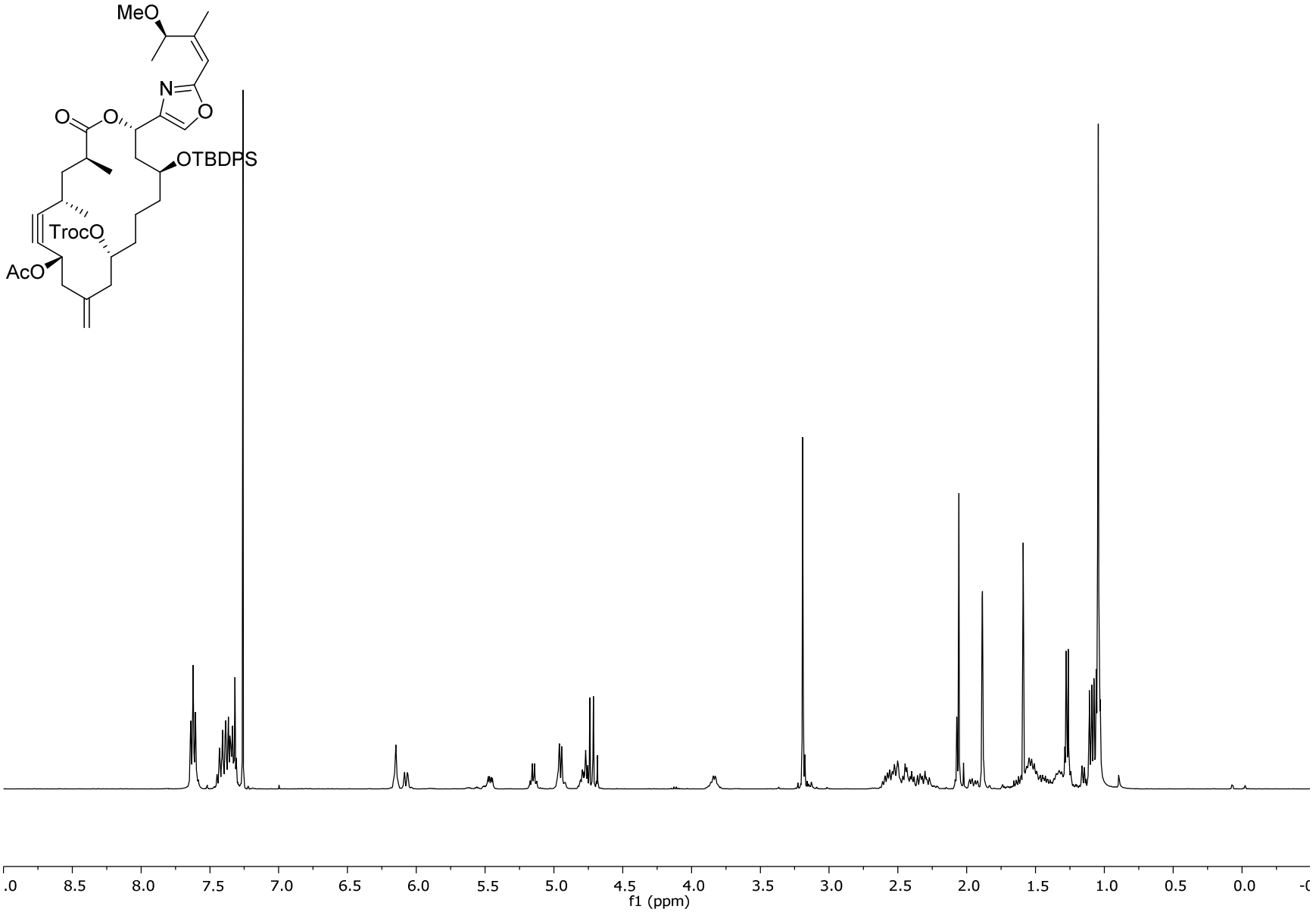
f1 (ppm)


MeO
N
O
O
O
OTBDPS
TrocO
AcO
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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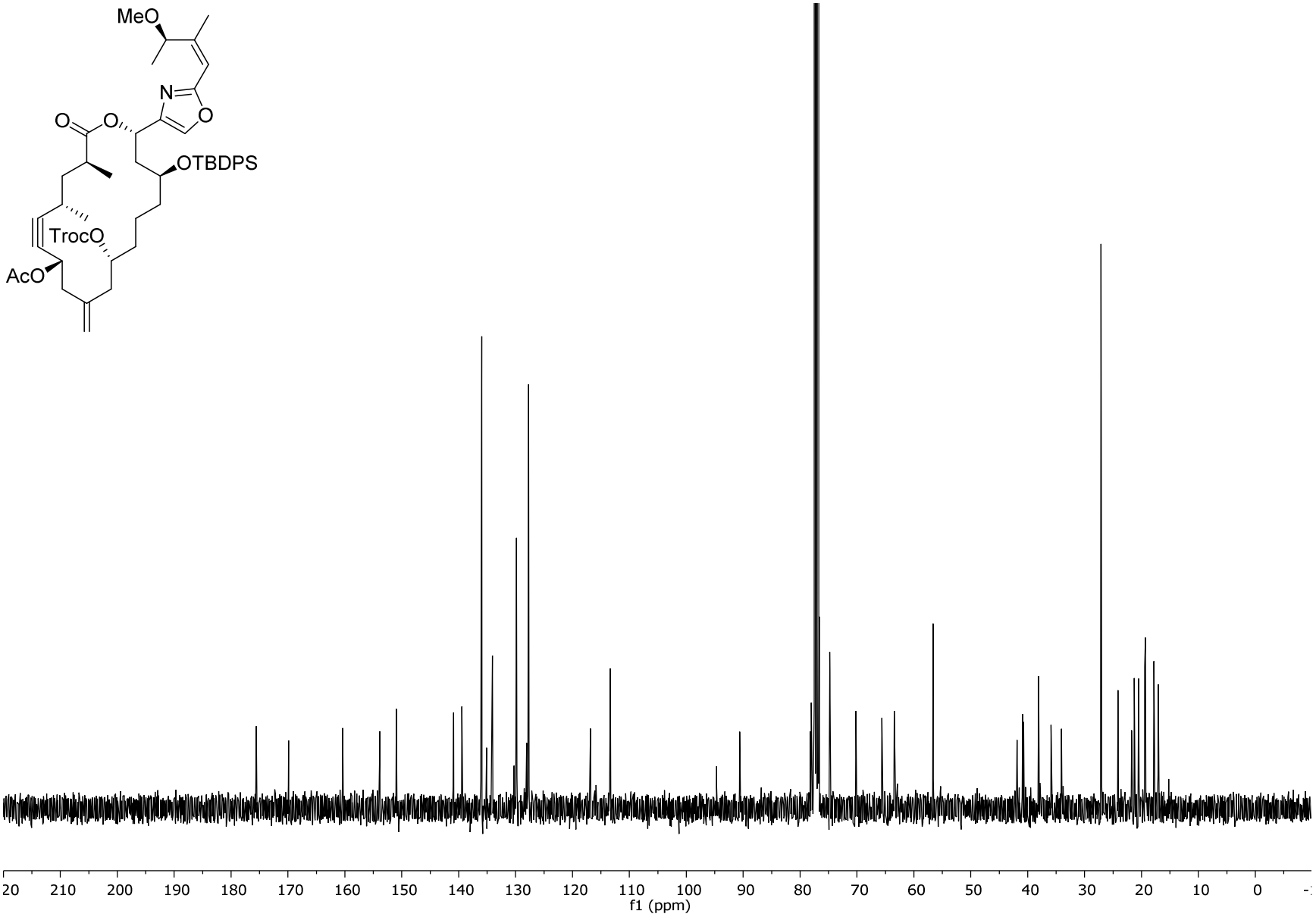
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


MeO
N
O
O
O
OTBDPS
TrocO
AcO
20
210
200
190
180
170
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150
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130
120
110
100
90
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70
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50
40
30
20
10
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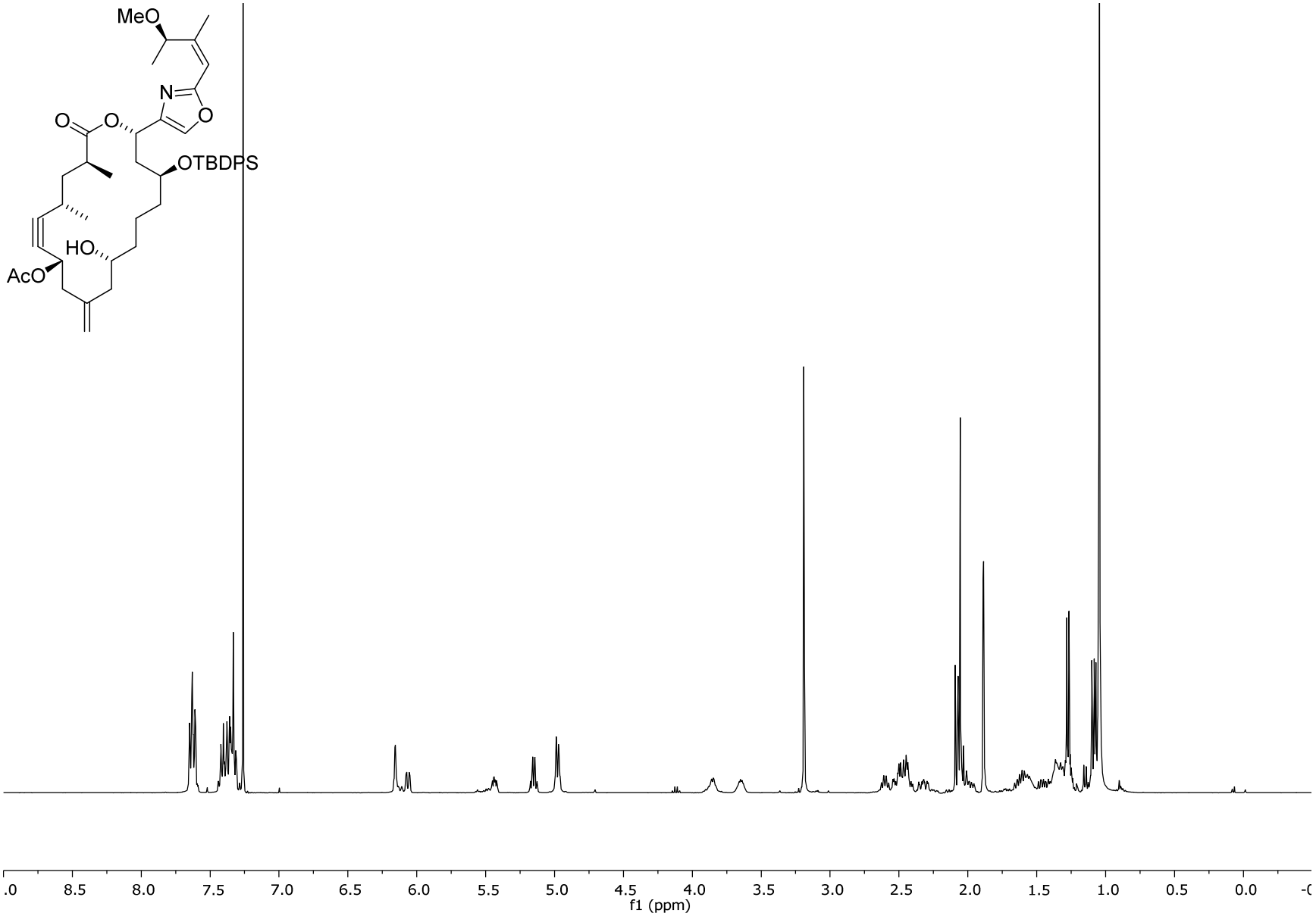
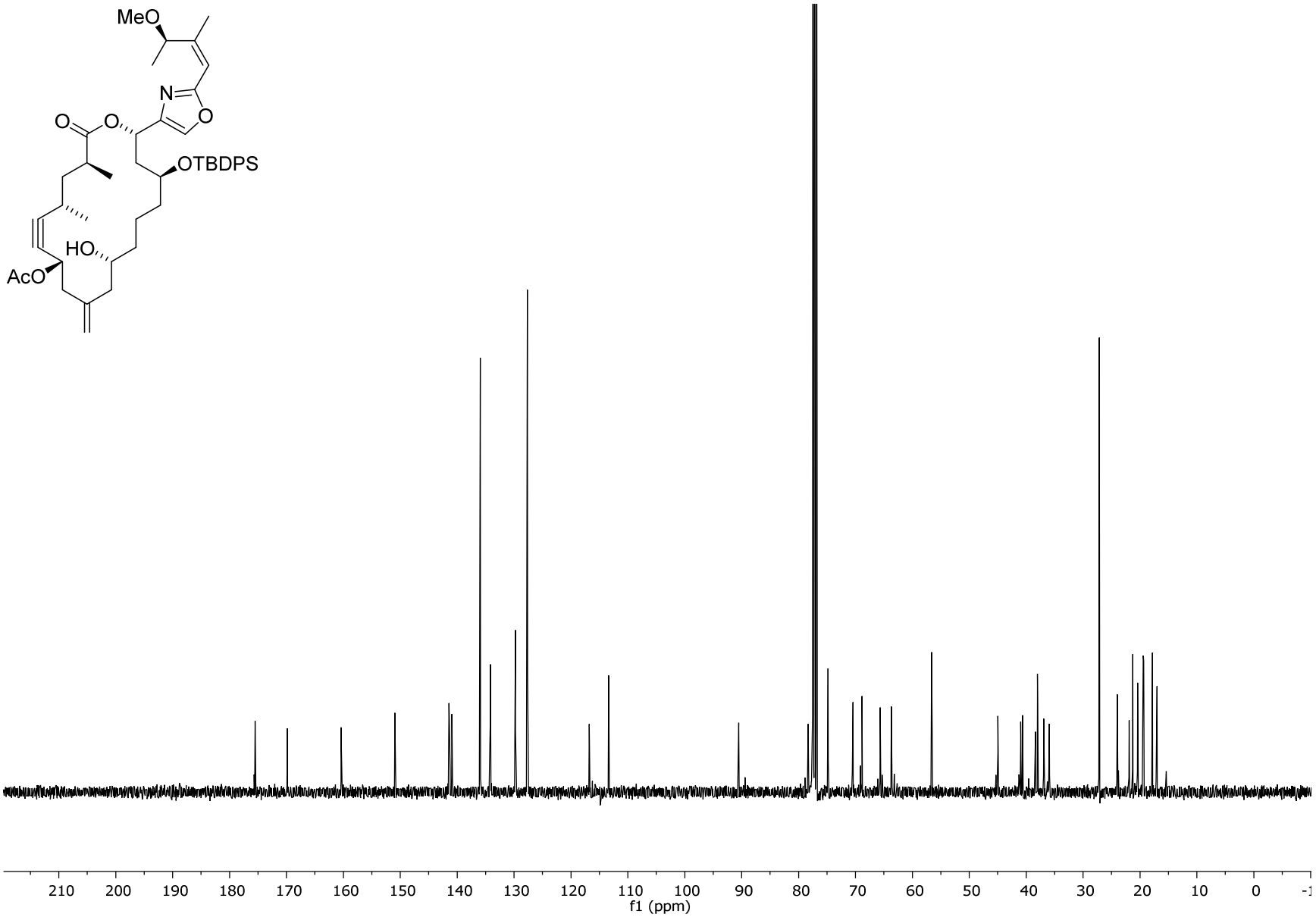
f1 (ppm)


MeO
N
O
O
O
OTBDPS
HO
AcO
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


MeO
N
O
O
O
OTBDPS
HO
AcO
210
200
190
180
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150
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130
120
110
100
90
80
70
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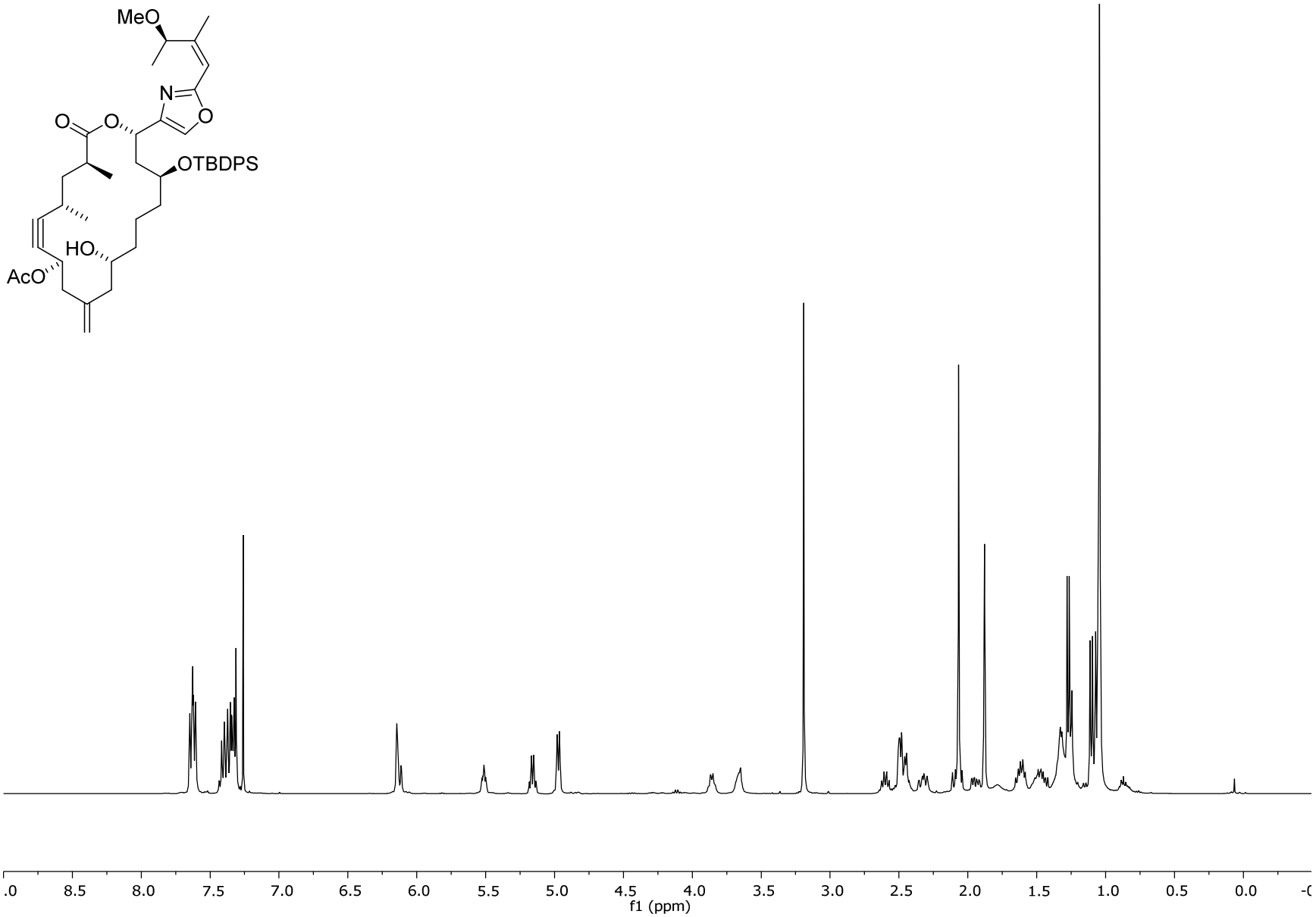
50
40
30
20
10
0
f1 (ppm)


MeO
N
O
O
O
OTBDPS
HO
AcO
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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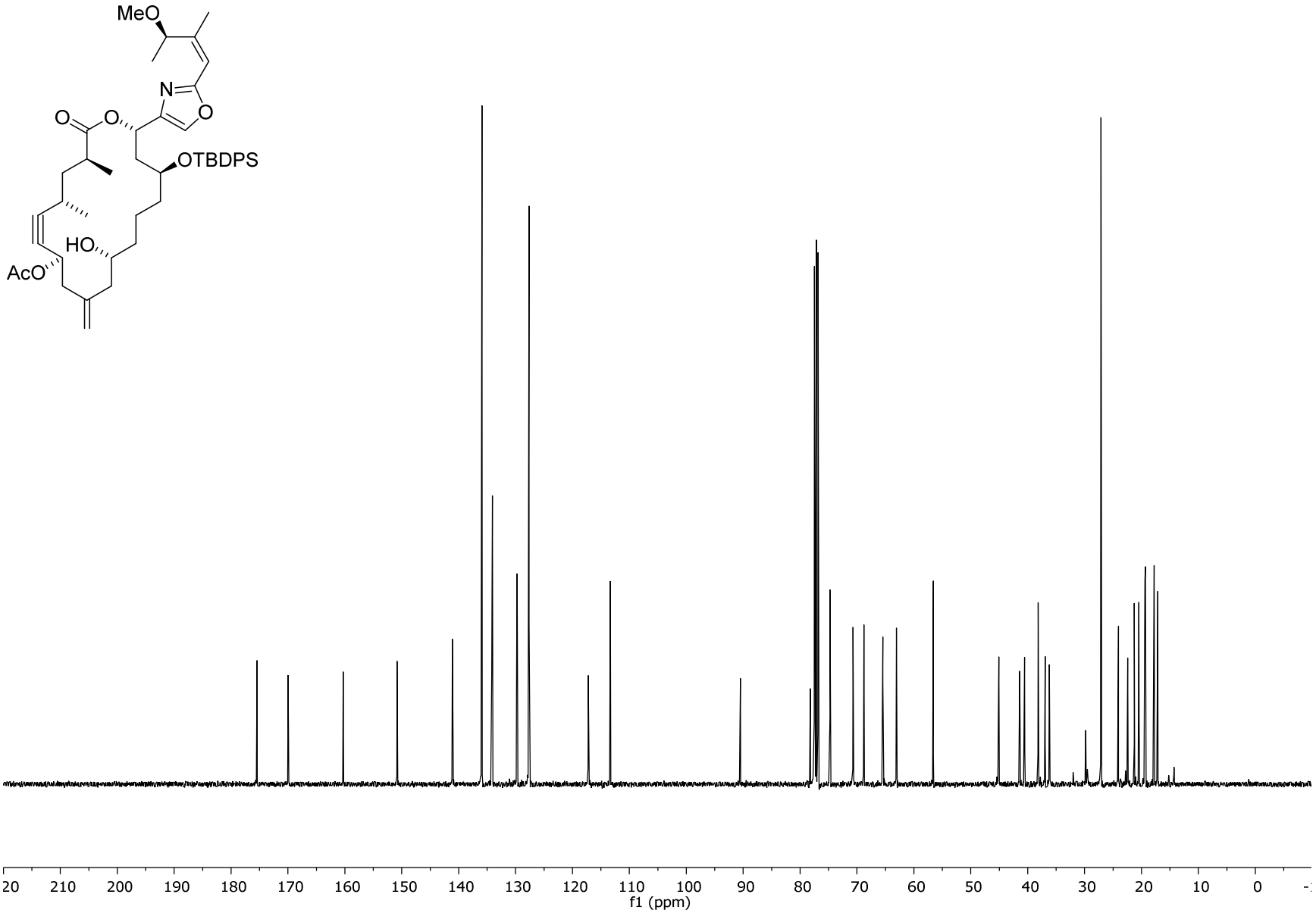
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


MeO
N
O
O
O
OTBDPS
HO
AcO
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190
180
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40
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10
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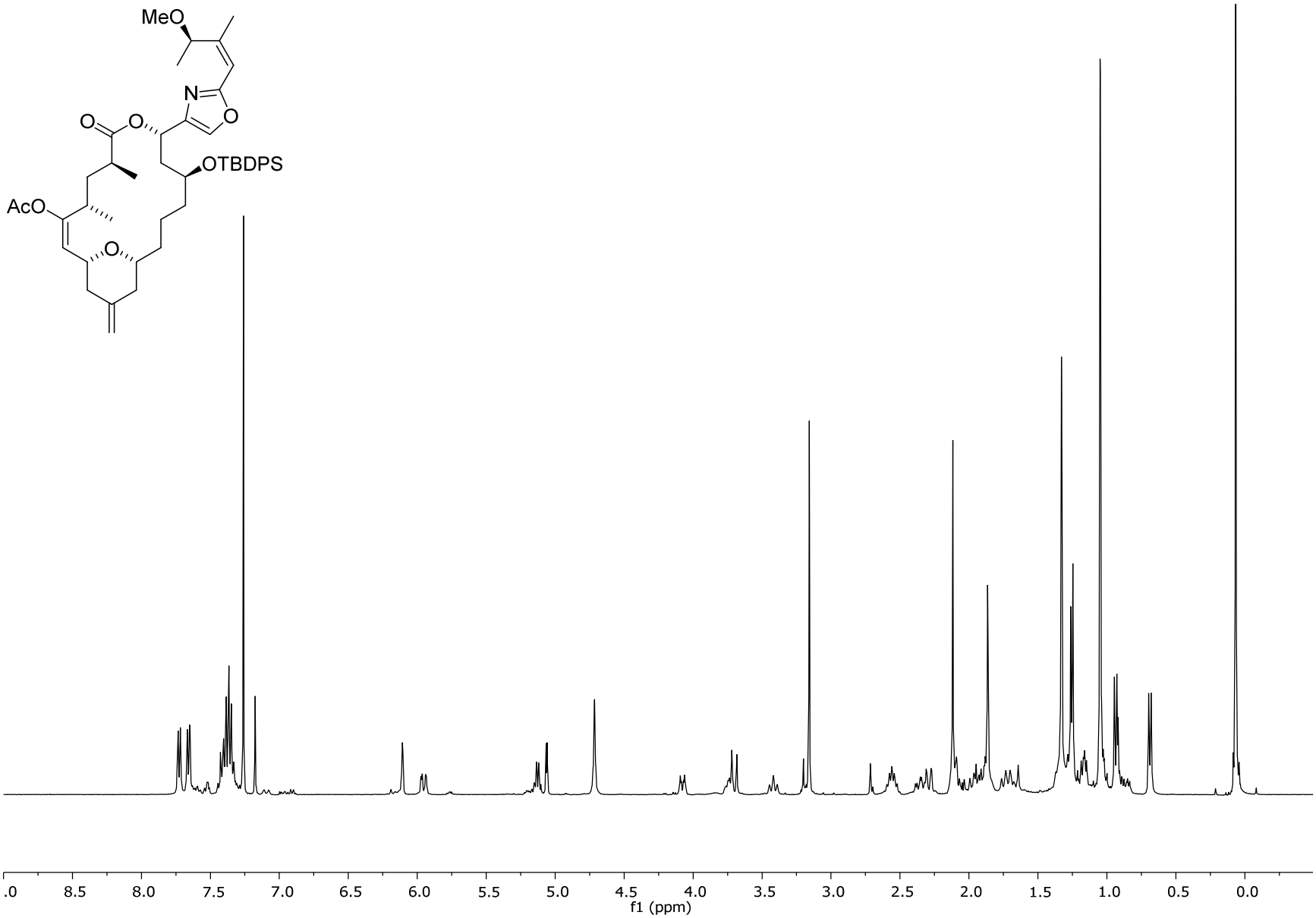
f1 (ppm)


MeO
N
O
O
O
OTBDPS
AcO
O
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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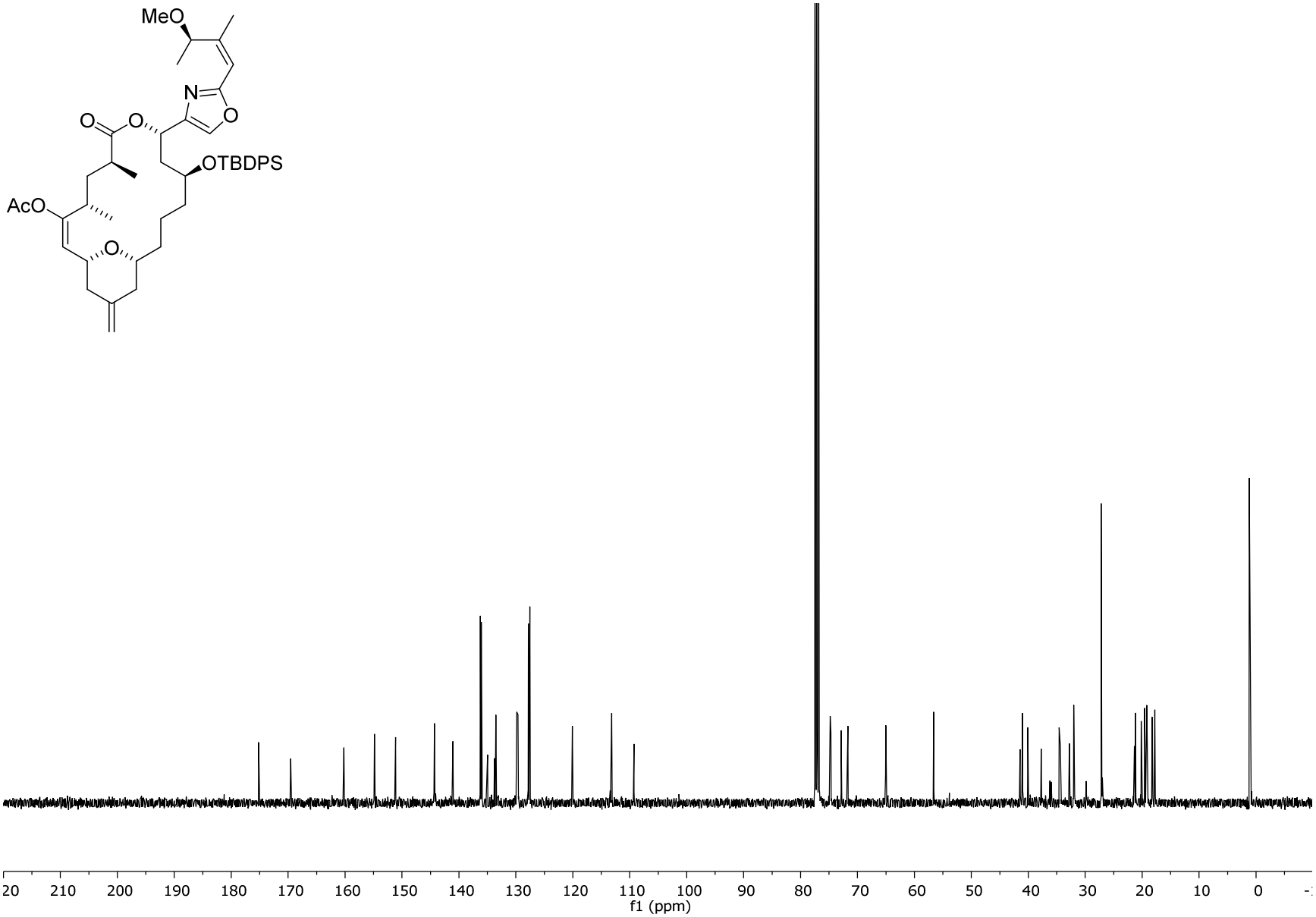
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


MeO
N
O
O
O
OTBDPS
AcO
O
220
210
200
190
180
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160
150
140
130
120
110
100
90
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70
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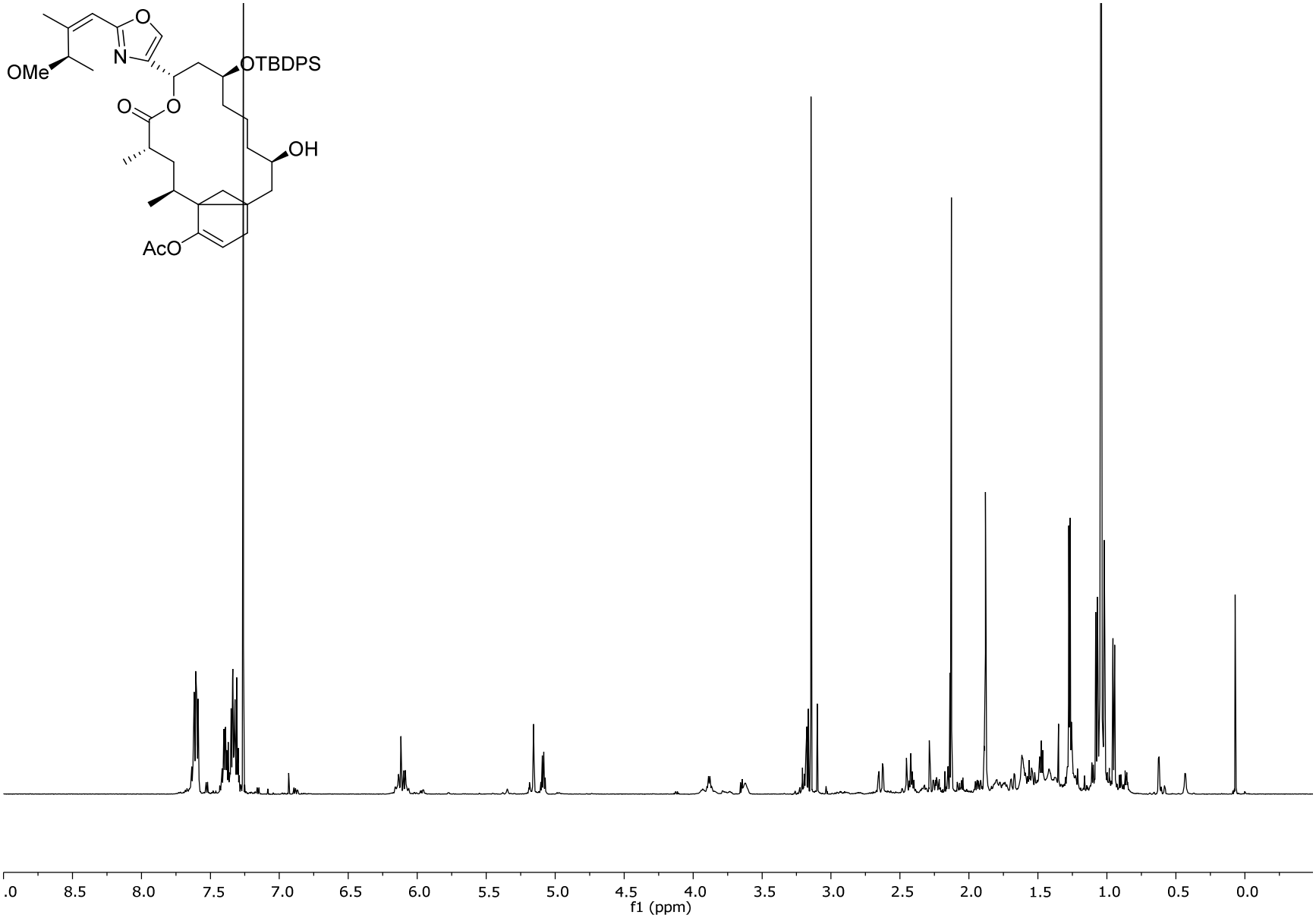
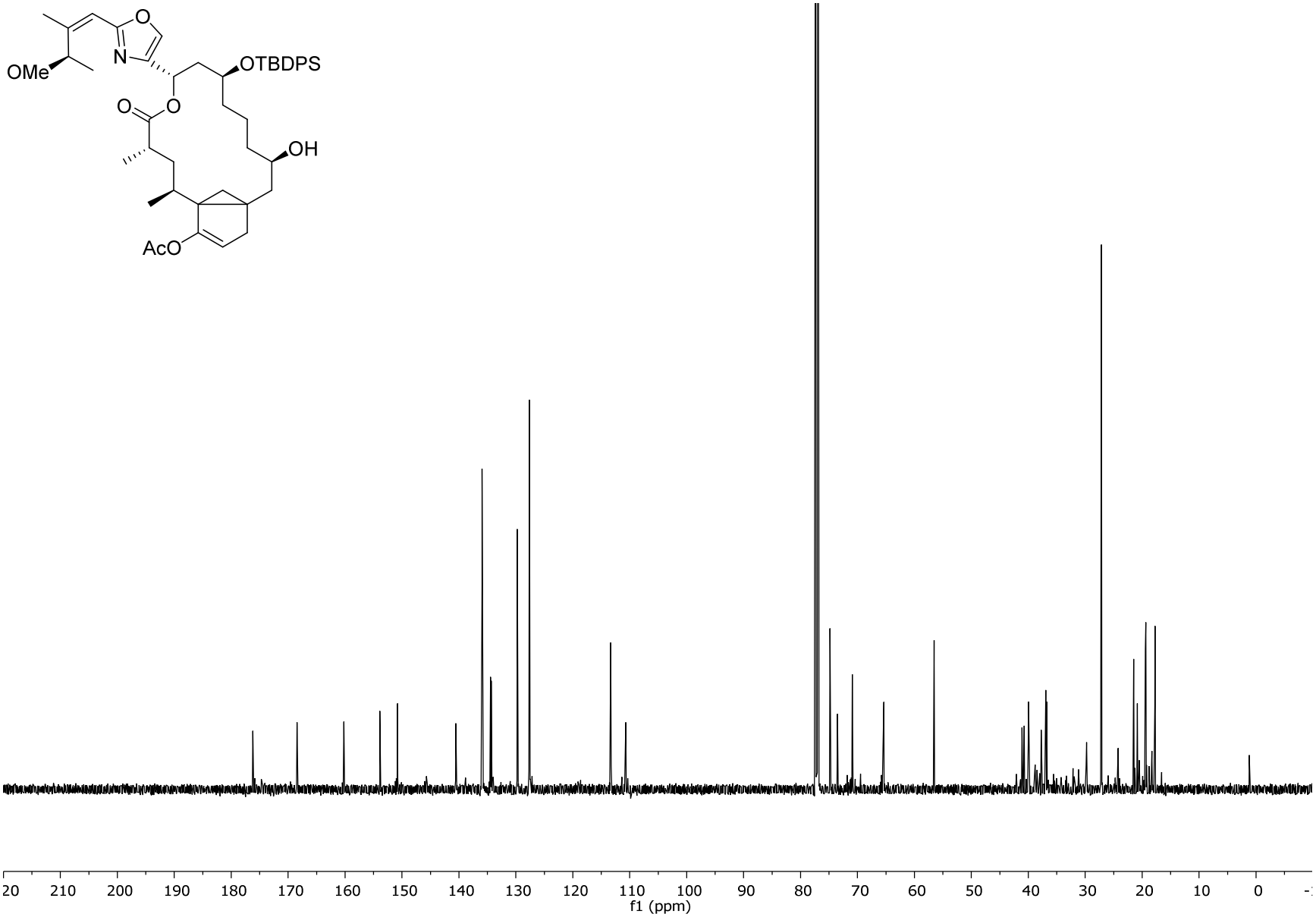
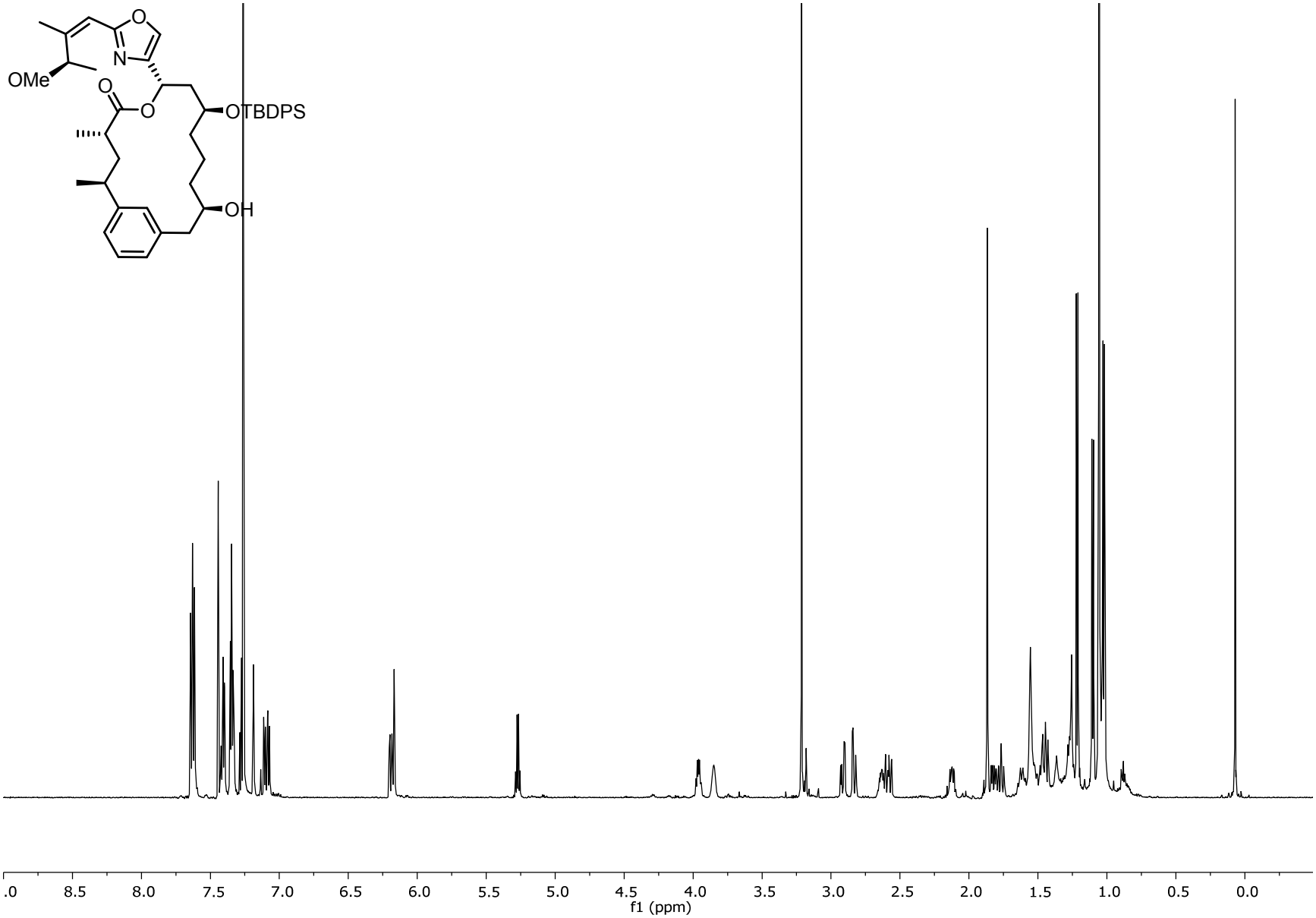
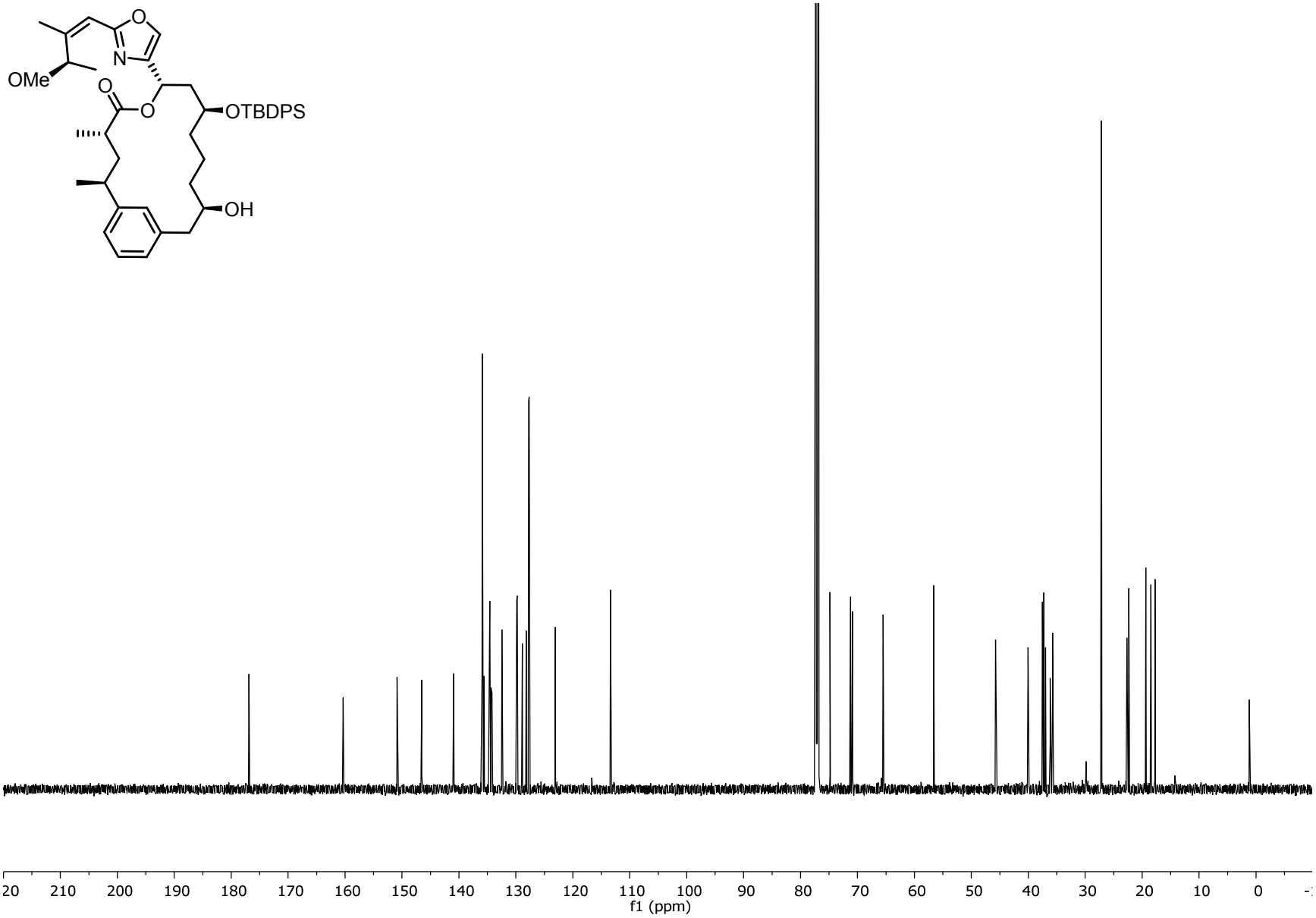
50
40
30
20
10
0
f1 (ppm)


OMe
O
N
OTBDPS
O
O
OH
AcO
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OMe
O
N
OTBDPS
O
O
OH
AcO
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OMe
O
N
O
O
OTBDPS
OH
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OMe
O
N
O
O
OTBDPS
OH
20
210
200
190
180
170
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150
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130
120
110
100
90
80
70
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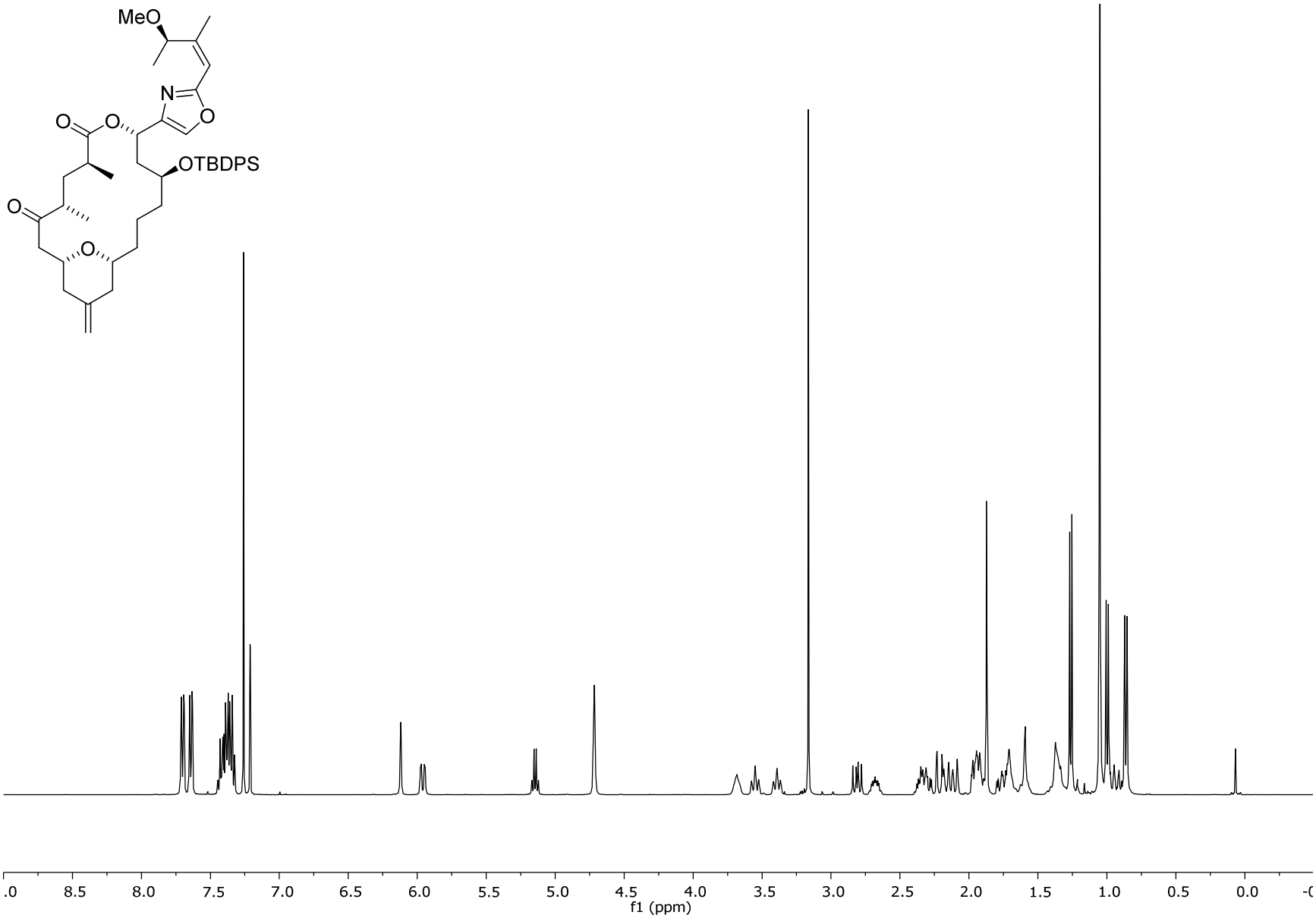
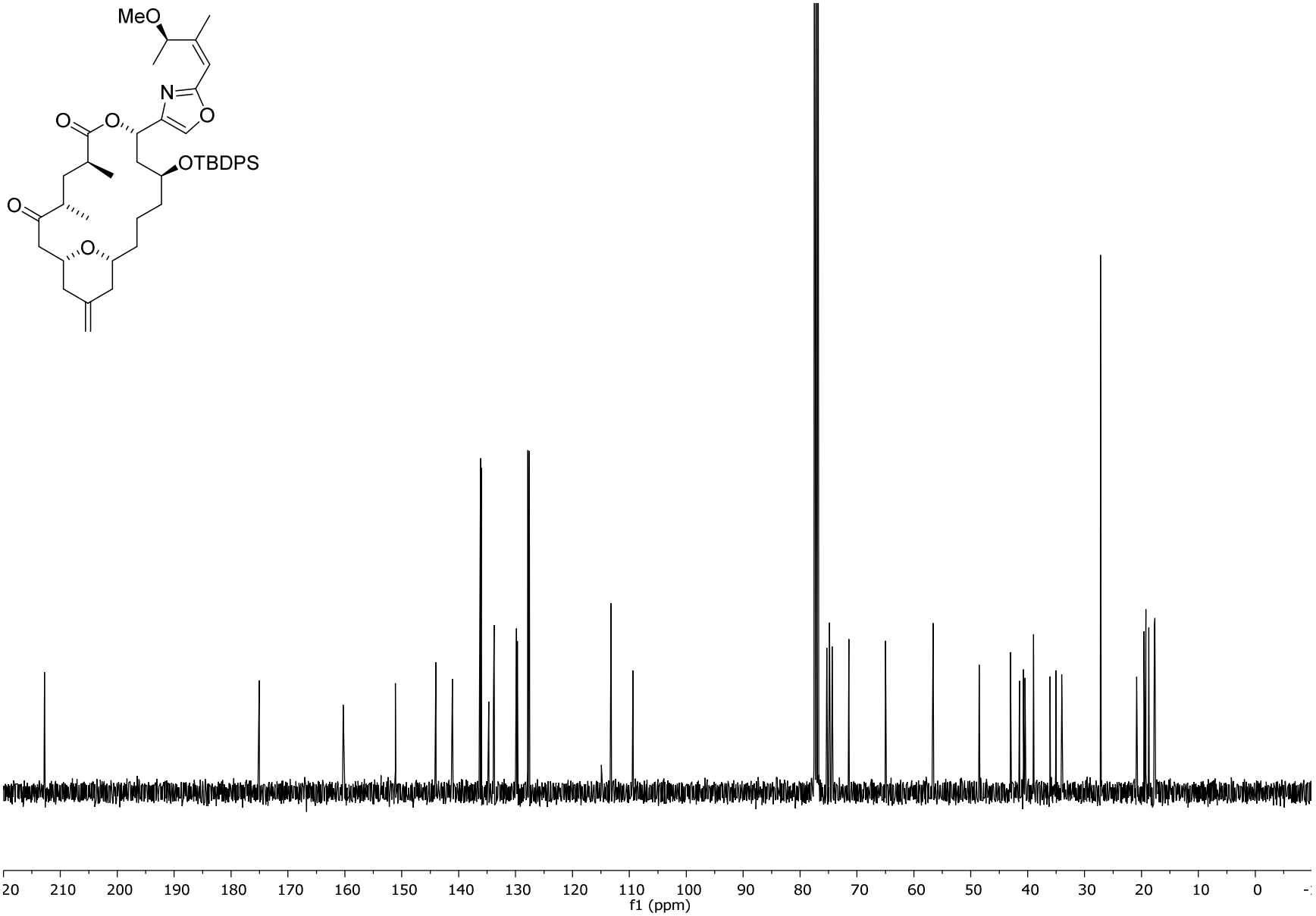
50
40
30
20
10
0
f1 (ppm)


MeO
N
O
O
O
OTBDPS
O
O
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


MeO
N
O
O
O
OTBDPS
O
O
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
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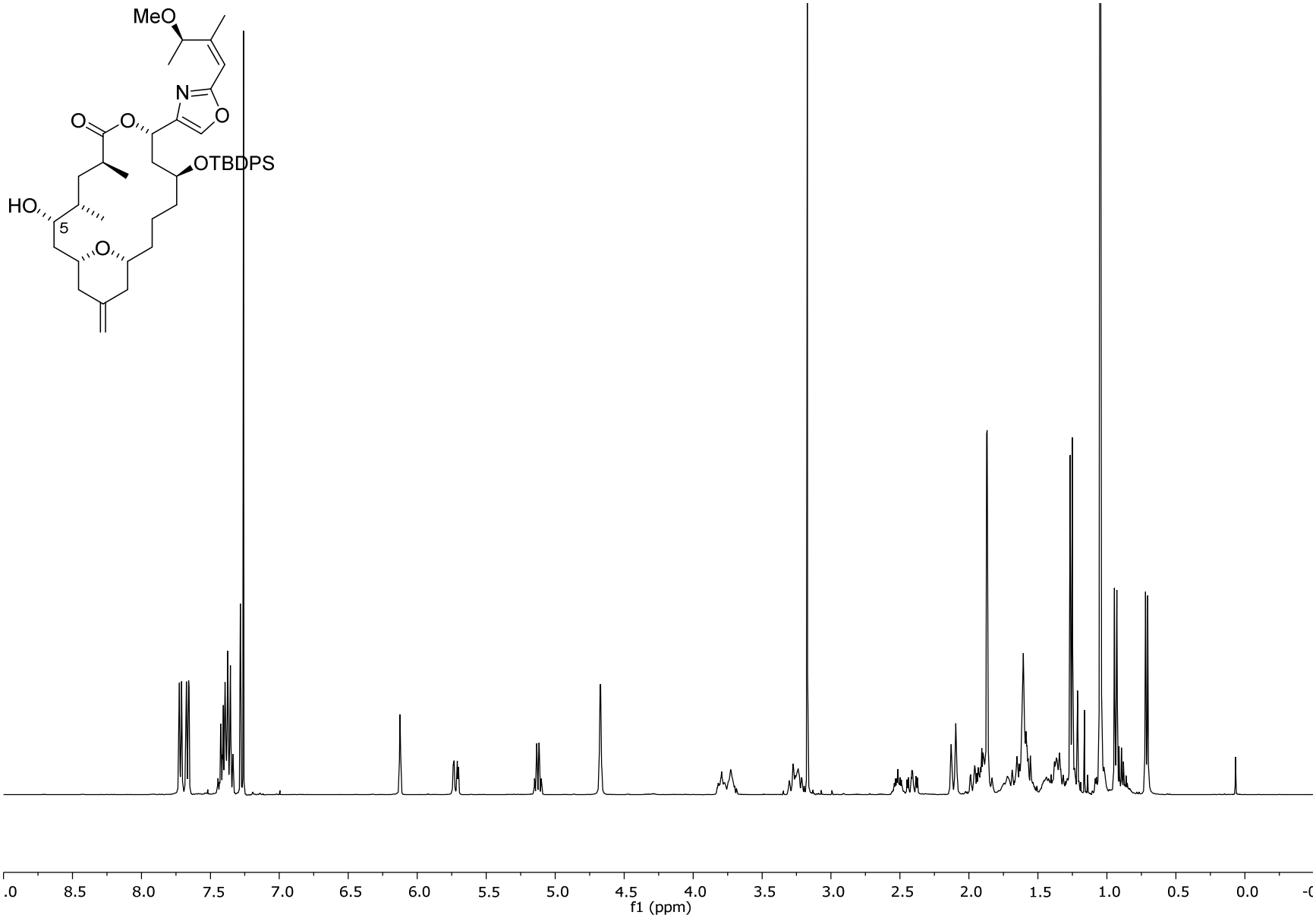
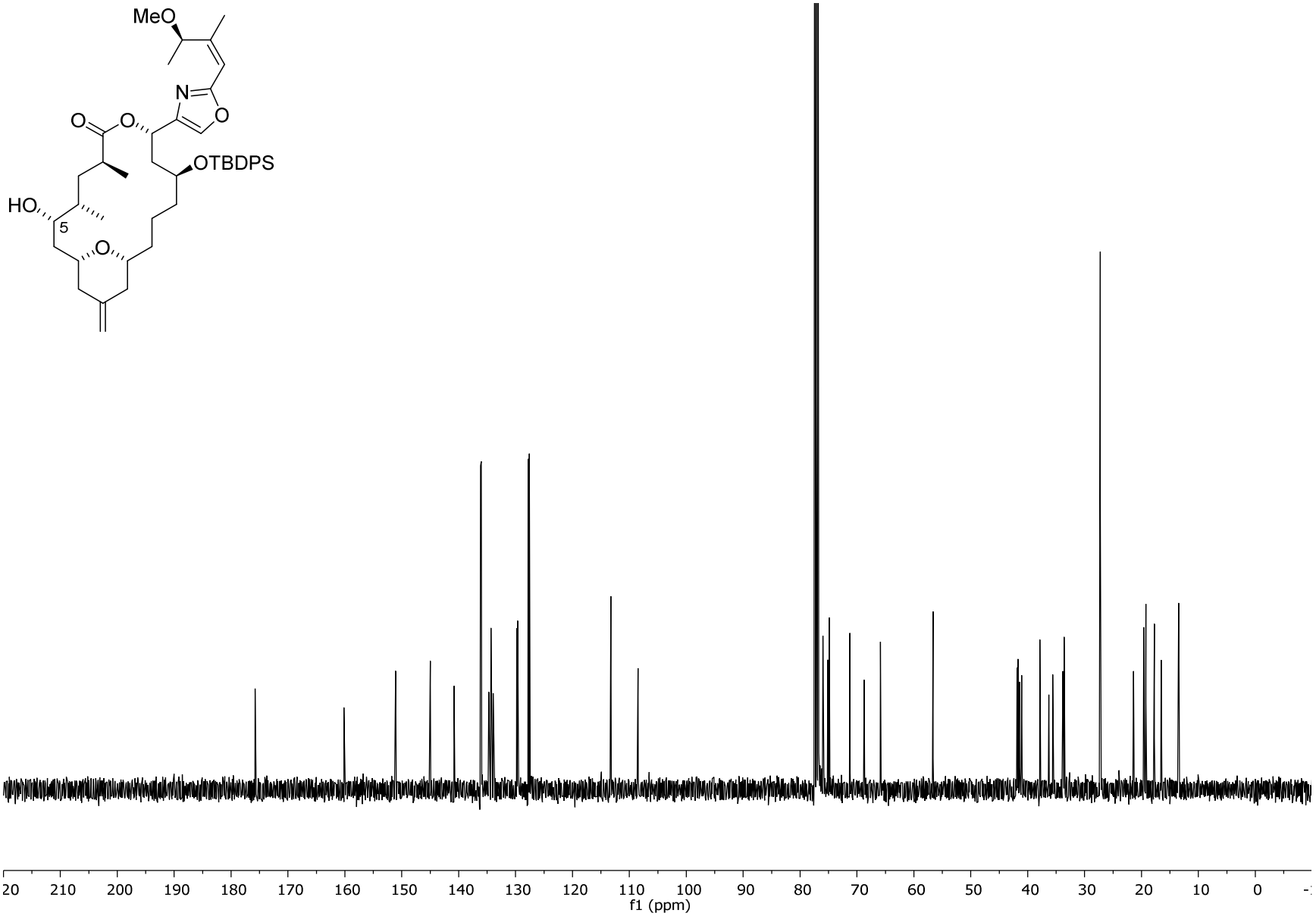
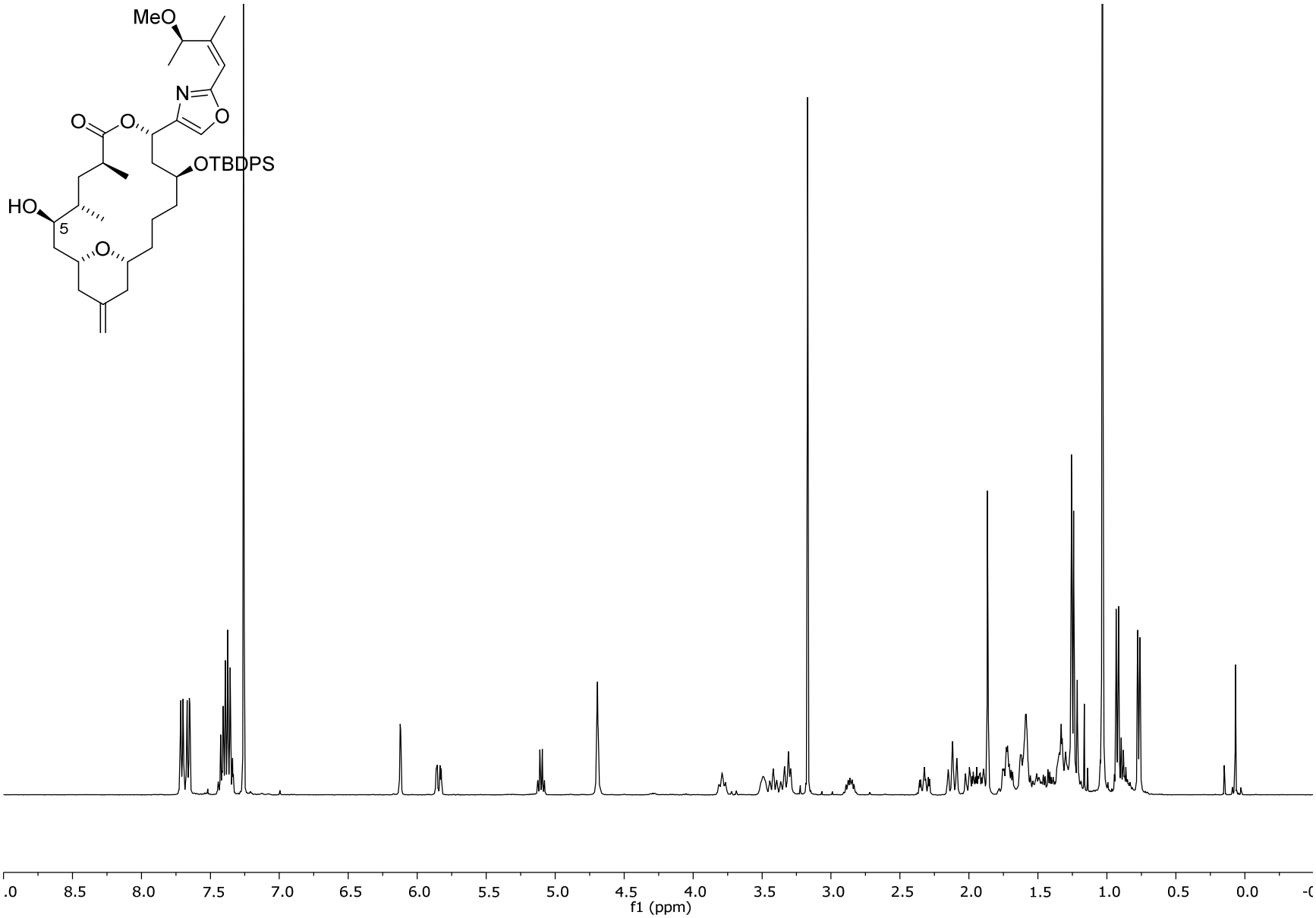
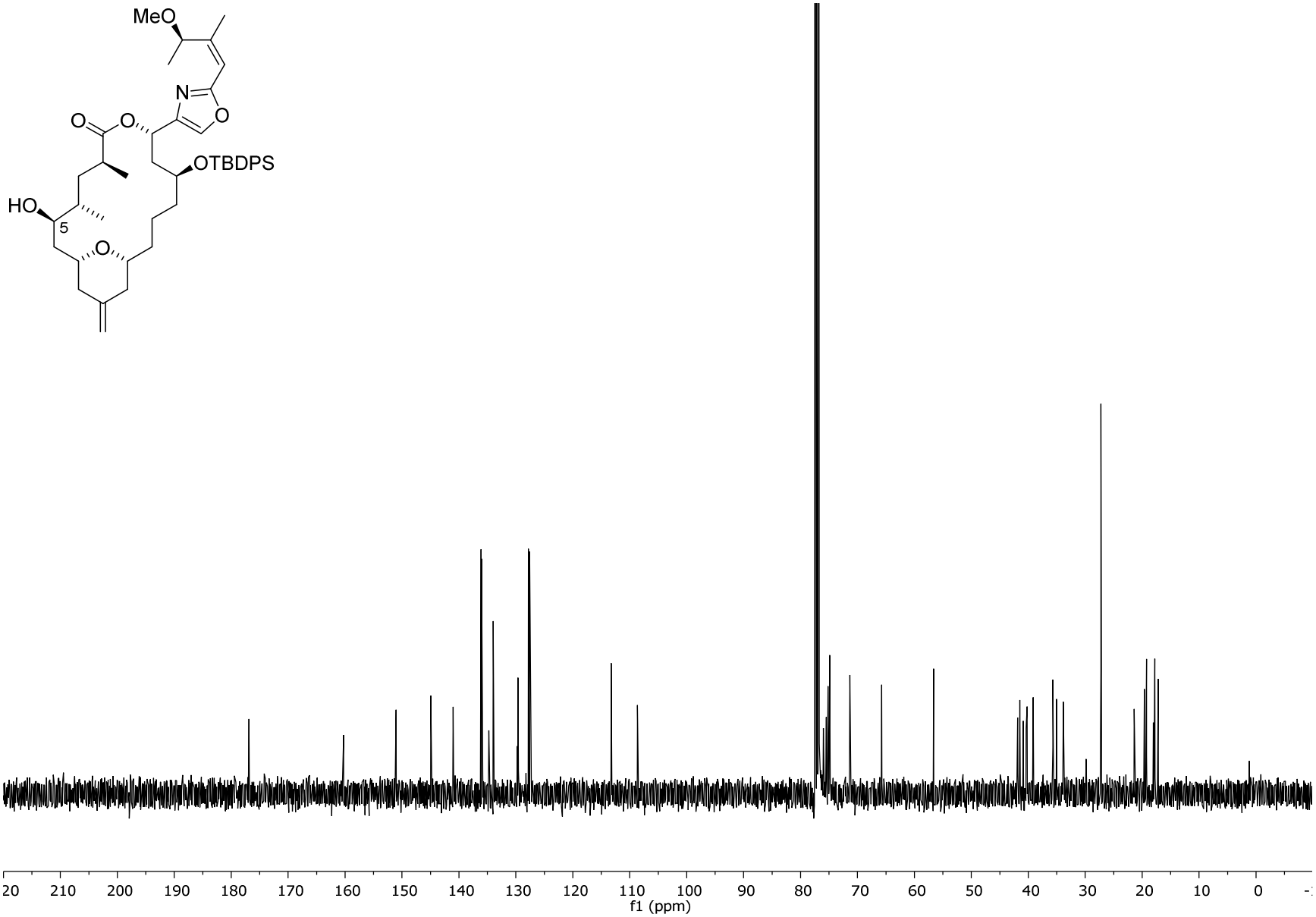
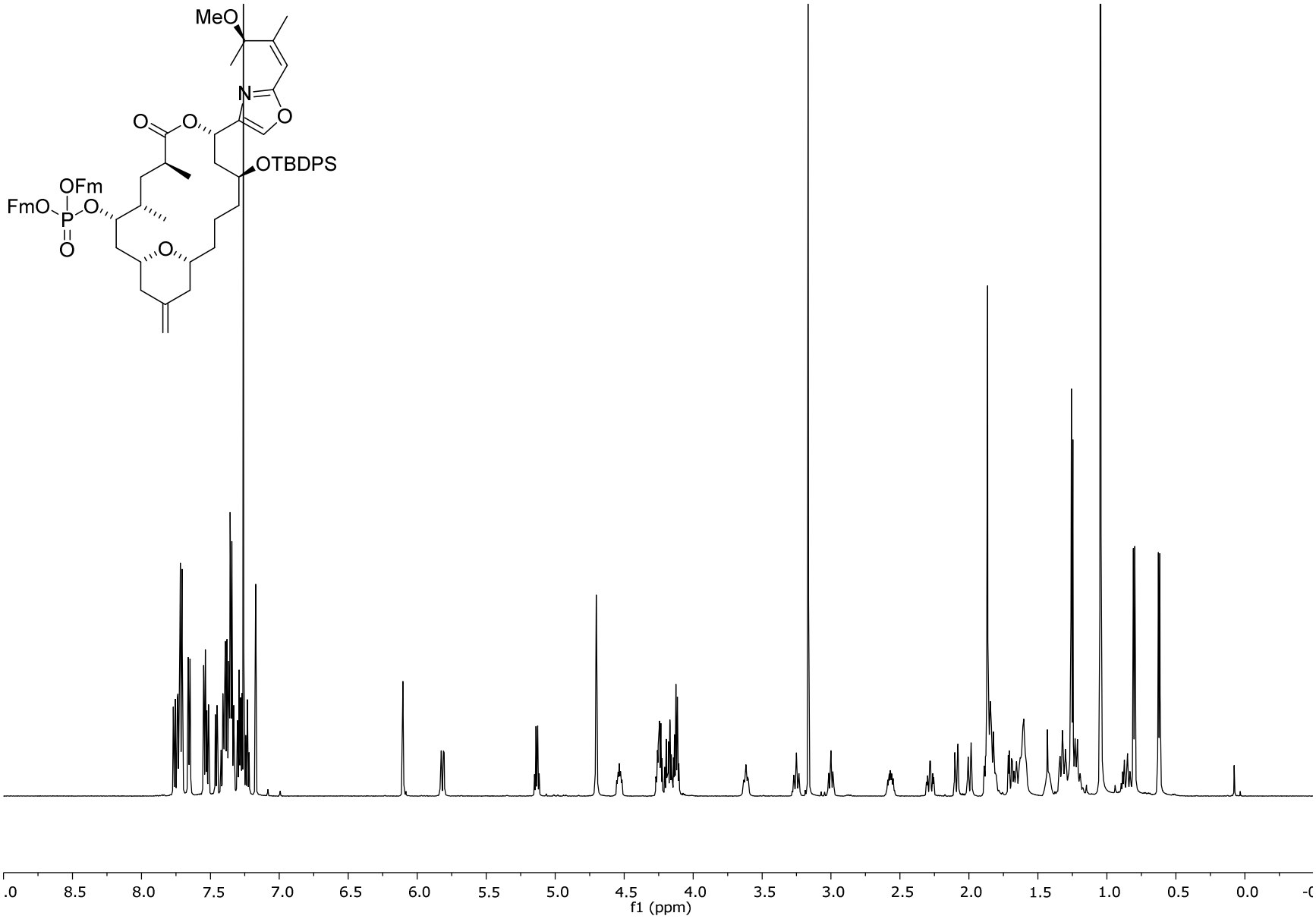
50
40
30
20
10
0
f1 (ppm)

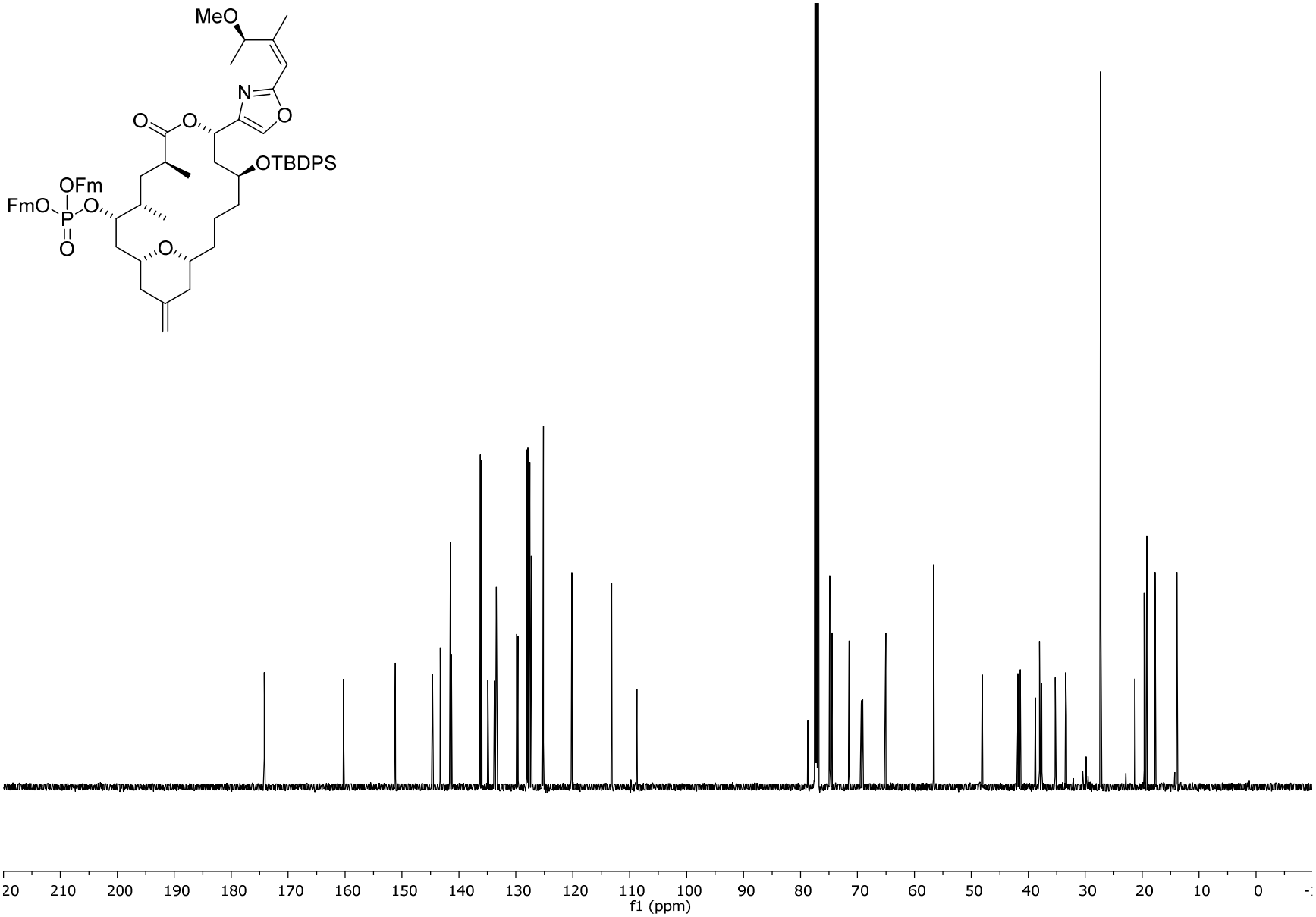

MeO
N
O
O
O
OTBDPS
HO
5
O
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

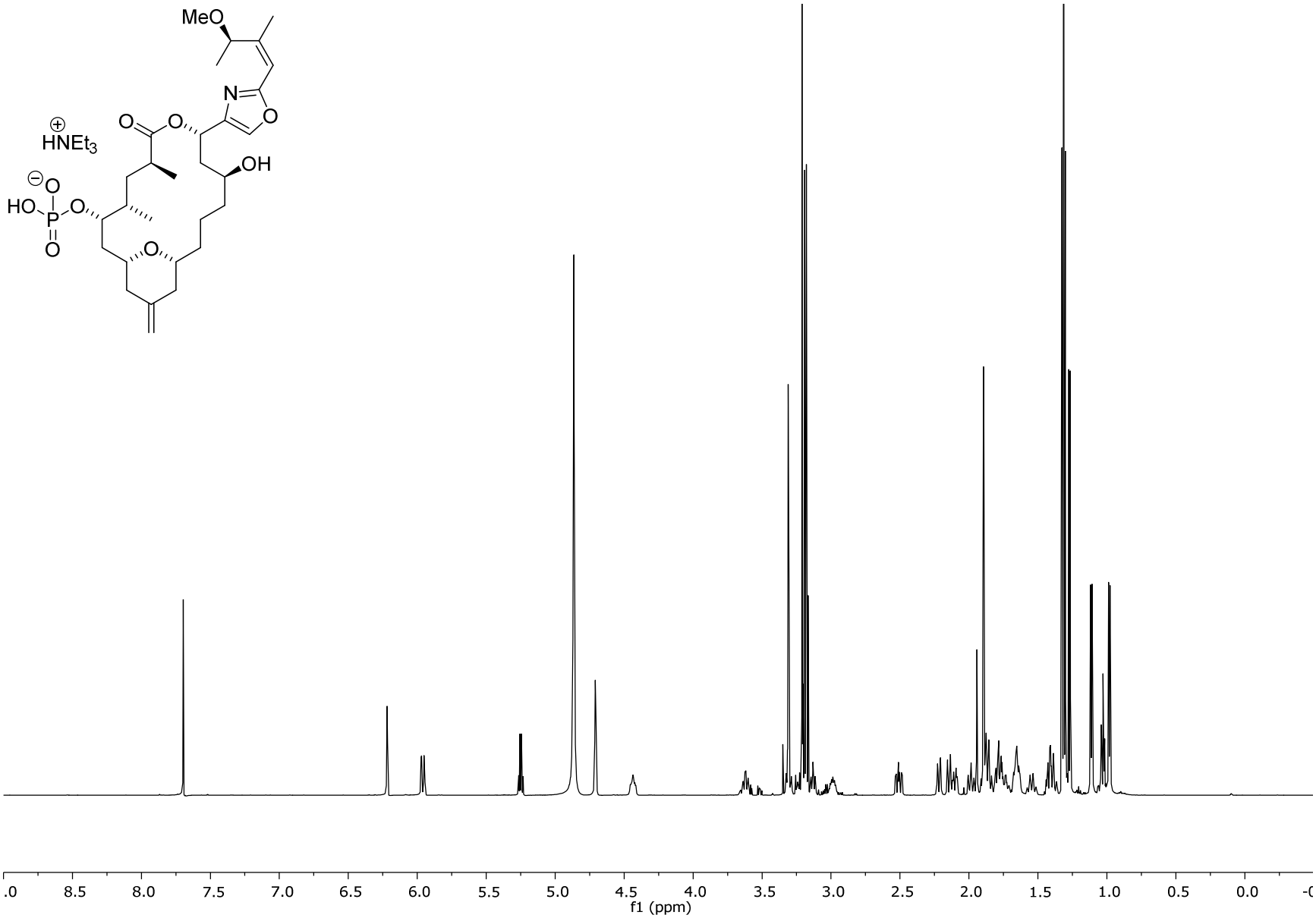

MeO
N
O
O
O
OTBDPS
HO
5
O
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

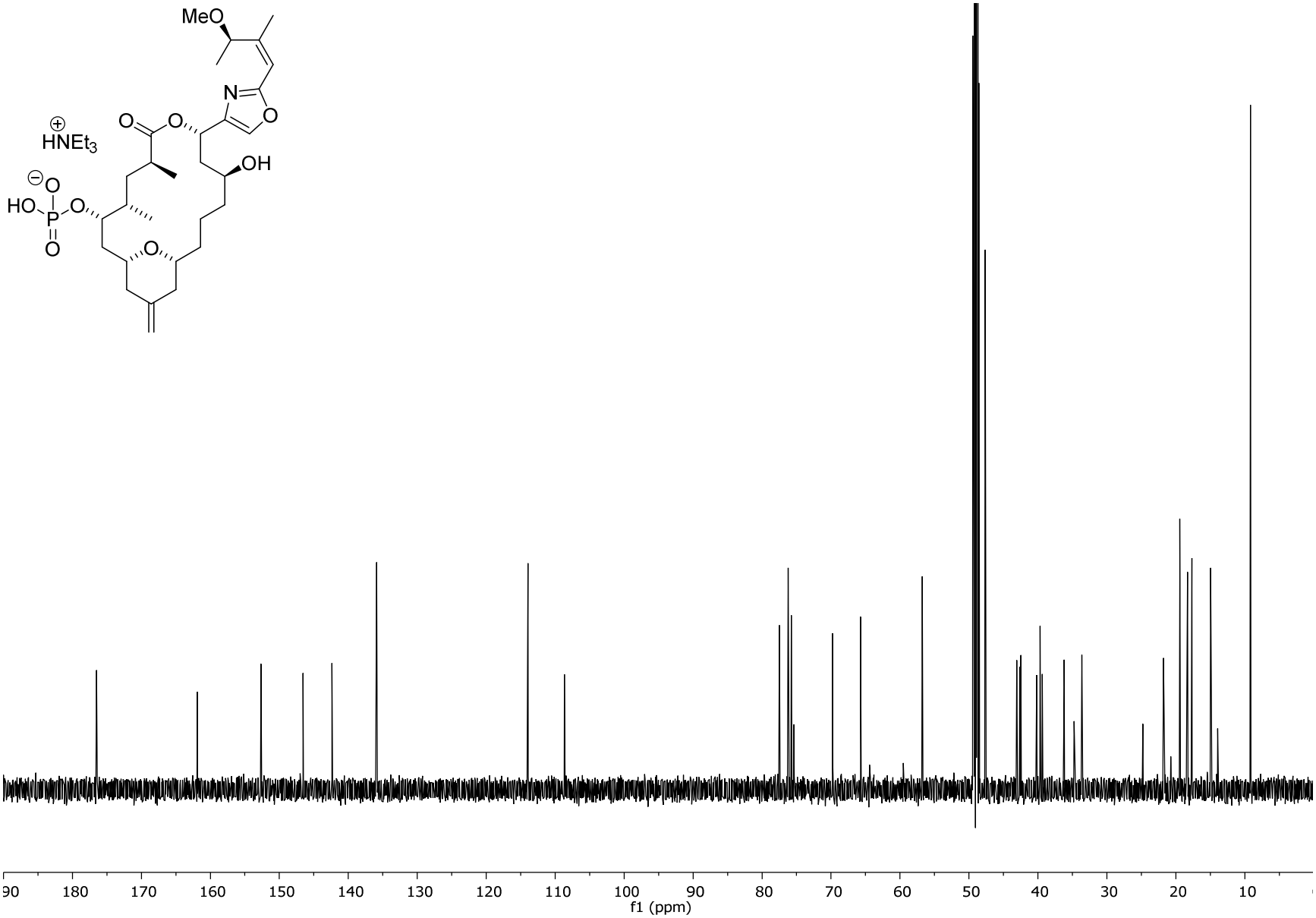

MeO
N
O
O
O
OTBDPS
HO
5
O
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

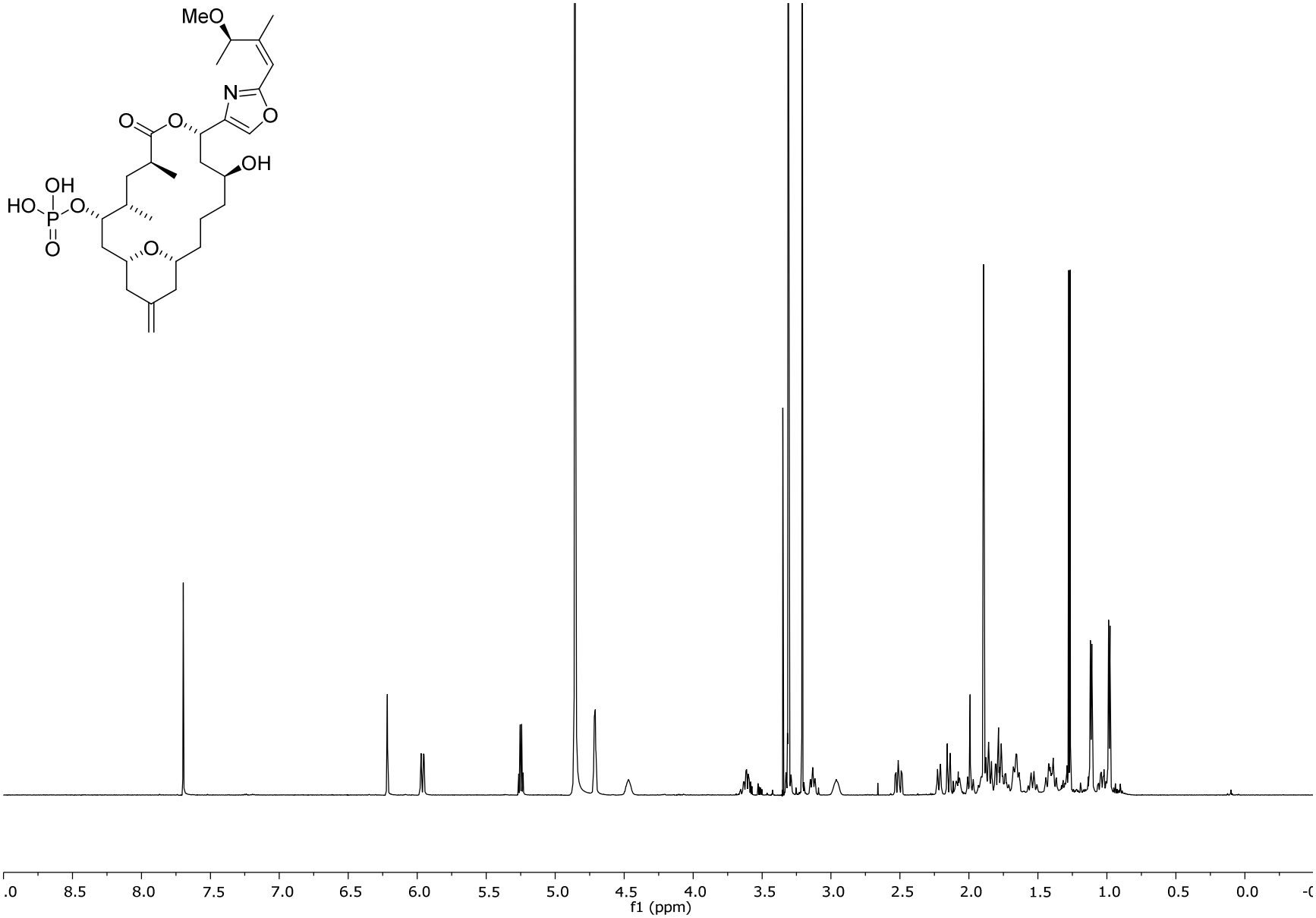

MeO
N
O
O
O
OTBDPS
HO
5
O
f1 (ppm)

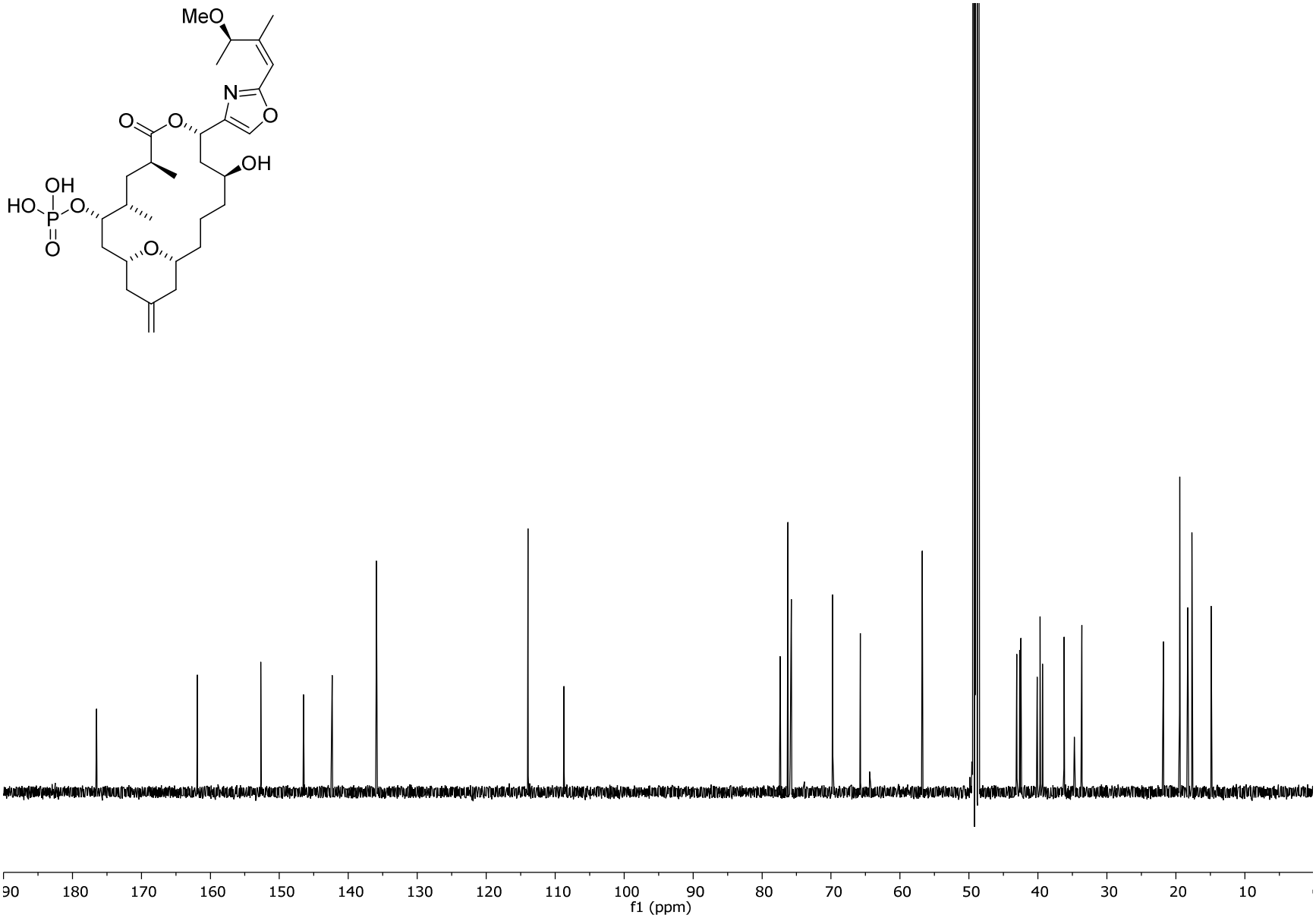

MeO
N
O
O
O
OTBDPS
OFm
FmO
P
O
O
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

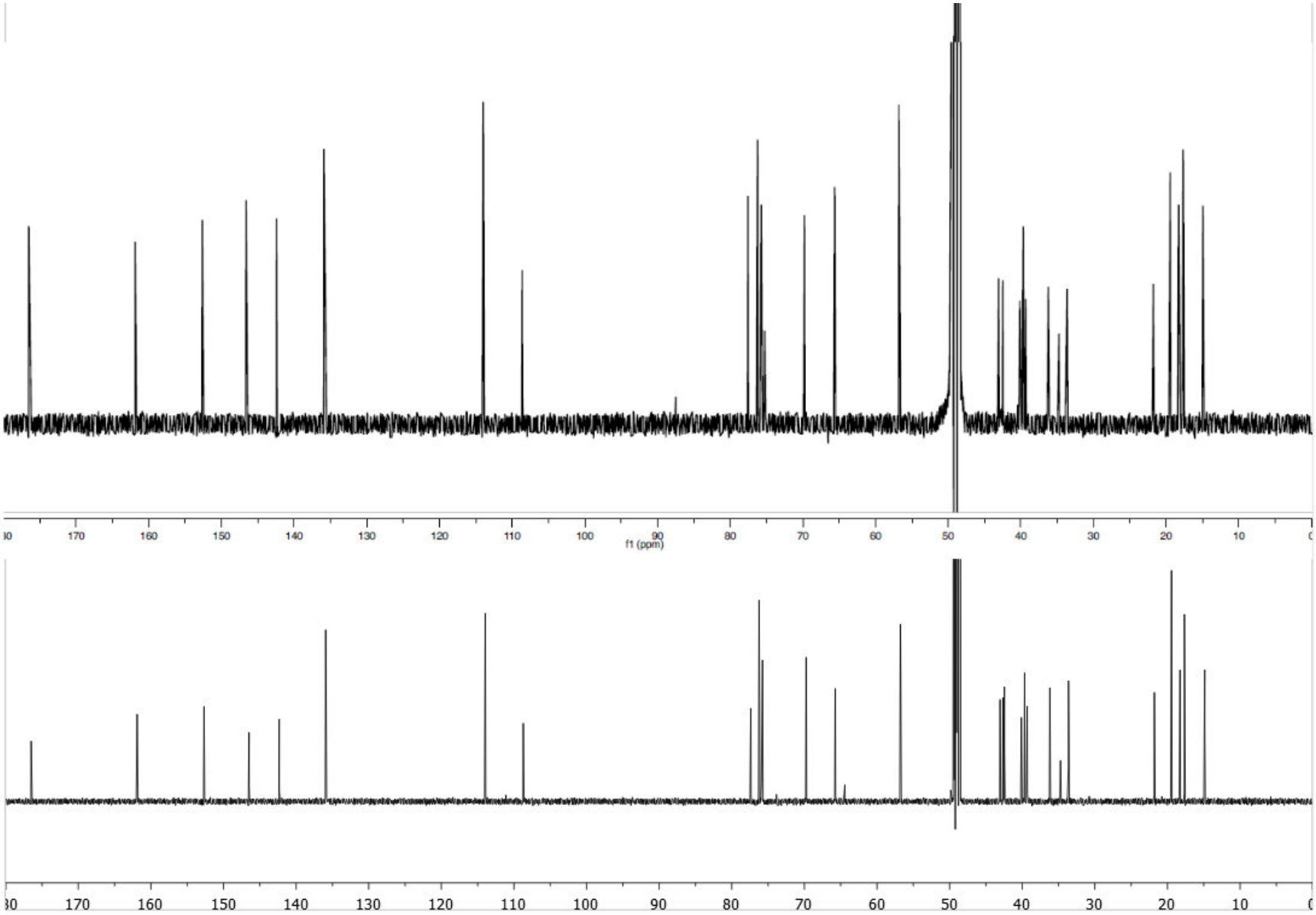

MeO
N
O
O
O
OTBDPS
OFm
FmO
P
O
O
O
O
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MeO
N
O
O
O
OH
HNEt3
HO
P
O
O
O
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


MeO
N
O
O
O
OH
HNEt3
HO
P
O
O
O
O
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


MeO
N
O
O
O
OH
HO
OH
P
O
O
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


MeO
N
O
O
O
OH
HO
OH
P
O
O
O
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



Comparison of Molinski's ^{13}C NMR (top) and Fürstner's (bottom)